Epidemiological Studies of Adiposity and Health Outcomes in Later Life

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I certify that all material in this thesis which is not my own work has been identified and that no material has previously been submitted and approved for the award of a degree by this or any other University.

Signature: ……...

Abstract

Globally, there has been a substantial rise in the prevalence of obesity amongst older persons (≥65 years) since the 1980s. Conflicting evidence exists on the impact of this trend for health outcomes. A 2013 meta-analysis documented no statistical difference for mortality between those within the body mass index (BMI) defined Obese-1 (30.0-34.9 kg/m^2) range and those within the conventional BMI Normal (18.5-24.9) range, sparking vigorous debate. The reduced or similar mortality risks for those within the BMI Obese-1 range relative to those within the BMI Normal range has been termed the "obesity paradox". Clarifying associations of obesity with health outcomes could have implications for intervention in later life. I aimed to examine this paradox by assessing the length of follow-up, the BMI referent group, the inclusion of smokers plus those with conditions associated with weight loss, and alternative measures of adiposity.

I analysed >955,000 electronic health records from the UK Clinical Practice Research Datalink for patients aged ≥60 years. I showed reduced mortality risks for those within the BMI Obese-1 range relative to those within the BMI Normal range across each age group. Mortality risks were reversed after restricting the analysis to 'healthier agers', demonstrating that the paradox is partly explained by the inclusion of smokers, adults with conditions associated with weight loss, and the chosen BMI referent group. Similarly, I document no support for reduced dementia risks for those within the BMI Obese-1 range. Additionally, there was an increased risk for incident of coronary heart disease and diabetes for those within the BMI Obese-1 range.

BMI does not capture body composition changes with ageing. I found additional adiposity measures improved the mortality prediction compared to BMI only using the UK Biobank comprising >200,000 older volunteers. Mortality risks were increased for those who were centrally obese across the BMI Normal to Obese-1 range.

In conclusion, I have shown the heterogeneity of older adults can result in disparate risk estimates for the association between BMI and health outcomes. I

Abstract

provide additional evidence that reliance on BMI measures only may miss those at increased risk for health outcomes due to central adiposity. My results provide no support, in relatively healthy older adults, for the hypothesised obesity paradox in later life.

Table of Contents

List of Tables

List of Tables

List of Tables

List of Tables

List of Figures

List of Figures

List of Figures

List of Tables for Supplementary Material

List of Figures for Supplementary material

List of Texts for Supplementary material

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Author's declaration

I confirm that this thesis is my original work. Where chapters have been based on published material this has been indicated. I would like to thank all the co-authors of these papers for their support and guidance which included advice on statistical techniques and improvements to study designs.

List of abbreviations

Abbreviation	
AIC	Akaike Information Criterion
AD	Alzheimer's Disease
ADL	Activities of Daily Living
AF	Atrial Fibrillation
BIA	Bioelectrical Impedance Analysis
BF	Body Fat
BF%	Body Fat Percentage
BMD	Bone Mineral Density
BMI	Body Mass Index
CABG	Coronary Artery Bypass Grafting
CAD	Coronary Artery Disease
CHD	Coronary Heart Disease
CHF	Congestive Heart Failure
CI	Confidence Interval
COPD	Chronic Obstructive Pulmonary Disease
CPRD	Clinical Practice Research Datalink
CrI	Credible Interval
CT	Computerised Tomography/ Clinical Trial
CVD	Cardiovascular Disease
D	Dementia
DBP	Diastolic Blood Pressure
DM	Diabetes
DXA	Dual-energy X-ray Absorptiometry
FFM	Fat Free Mass
FFMI	Fat Free Mass Index
FH	Family history
FM	Fat Mass
FMI	Fat Mass Index
GP	General Practitioner

List of abbreviations continued

HC	Hip Circumference
HD	Heart Disease
HDL	High Density Lipoprotein
HE	Health Examination
HES	Hospital Episode Statistics
HF	Heart Failure
HGB	Hemoglobin
HR	Hazard Ratio
HRT	Hormone Replacement Therapy
HTN	Hypertension
IADL	Instrumental Activities of Daily Living
ICD	International Classification of Diseases
IHD	Ischemic Heart Disease
IQR	Inter-quartile Range
LDL	Low density Lipoprotein
LTPA	Leisure time Physical Activity
MET	Metabolic Equivalent of Task
MI	Myocardial Infarction
MRI	Magnetic Resonance Imaging
NHS	National Health Service
NICE	National Institute of Health and Excellence
NR	Not Reported
OB	Obese
ONS	Office for National Statistics
OR	Odds Ratio
PA	Physical Activity
QOF	The Quality and Outcomes Framework
RF	Renal Failure
SBP	Systolic Blood Pressure

List of abbreviations continued

SES	Socio-economic Status
SD	Standard Deviation
SHR	sub-Hazard Ratio
SM	Skeletal Mass
SMI	Skeletal Mass Index
T2D	Type 2 Diabetes
TIA	Transient Ischemic Attack
UI	Uncertainty Interval
VaD	Vascular Dementia
WBC	White Blood Cells
WC	Waist Circumference
WHR	Waist-to-hip Ratio
WHtR	Waist-to-height Ratio
WHO	World Health Organization

List of study abbreviations

Study abbreviation	
AGES-Reykjavik	Age, Gene/Environment, Susceptibility Reykjavik study
AHS-1	Adventist Health Study
AHS	Agricultural Health Study
ALSA	Australian Longitudinal Study of Ageing
ALSWH	Australian Longitudinal Study of Women's Health
BCDDP	The Breast Cancer Detection Demonstration Project
BLSA	Baltimore Longitudinal Study of Aging
CAIDE	Cardiovascular risk factors, Aging and Dementia (CAIDE)
CCSMHA	The Cache County Study of Memory Health and Aging
CHAMP	Concord Health and Ageing in Men Project
CHS	Cardiovascular Health Study
COMS	The Collaborative Ocular Melanoma Study
CTS	California Teachers Study
EPESE	Established Populations for Epidemiologic Studies of the Elderly
EPIDOS	Epidemiology of Osteoporosis
FHS	Framingham Heart Study
GRAS	Geisinger Rural Aging Study
HIMS	Health In Men Study
HRS	Health and Retirement Study
HSE	Health Survey for England
HPFS	Health Professionals Follow-up Study
ILSA	Italian Longitudinal Study on Aging

List of study abbreviations continued

IWHS	Iowa Women's Health Study
MCCS	Melbourne Collaborative Cohort Study
MELSHA	Melbourne Longitudinal Studies on Healthy Ageing
NHANES	National Health and Nutrition Examination Survey
NHIS	National Health Interview Study
NHS	Nurses' Health Study
NLTCS	National Long Term Care Survey
PHS	Physicians' Health Study
PLCO	Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial
PROSPER	Pravastatin in the Elderly at Risk
SALLS	Swedish Annual Level-of-Living Survey
SENECA	Survey in Europe on Nutrition and the Elderly; a Concerted Action
SMC	Swedish Mammography Cohort
THIN	The Health Improvement Network
USRT	United States Radiologic Technologists Study
VITAL	VITamin D and OmegA-3 TriaL
WHI	Women's Health Initiative
WHS	Women's Health Study
WLHS	Women's Lifestyle and Health Study

Chapter 1 Introduction

Table of Contents

List of Tables for Chapter 1

1.1. Background

Since 1975 there has been a substantial increase in the global prevalence of obesity; in 2014, 266 million men and 375 million women were estimated to be obese compared to 34 million men and 71 million women in 1975 (Di Cesare *et al.*, 2016). In 2013, the World Health Organization (WHO) published a global action plan to reduce health outcomes attributable to non-communicable diseases, including a target to halt the prevalence of obesity by 2025 to the 2010 level (World Health Organization, 2013).

Concurrent with the trend of rising obesity is an ageing population. Globally in 2015, 901 million people were aged ≥60 years and 125 million aged ≥80 years (United Nations, Department of Economic and Social Affairs, Population Division 2015). Obesity in older persons is emerging as a key public health issue with increasing numbers entering this life stage with values of body mass index (BMI) greater than that deemed healthy.

It is well established that younger and middle aged adults within the body mass index defined Obese-1 (30.0-34.9 kg/m^2) range are at an increased risk for cardiovascular disease, cancer, and mortality relative to those within the BMI Normal (18.5-24.9) range (Calle *et al.*, 1999; Adams *et al.*, 2006; Renehan *et al.*, 2007; Whitlock *et al.*, 2009; Wormser *et al.*, 2011). There is conflicting evidence, however, on the impact of the obesity trend for health outcomes in later life, specifically for mortality and dementia. Older persons within the BMI defined Obese-1 range have reportedly reduced or similar mortality risks relative to those within the BMI Normal range. This opposing mortality risk for the BMI Obese-1 range has been termed the 'obesity paradox'. There are several proposed contributors to this paradox in later life including:

- Inadequate control for confounders e.g. smoking
- Inadequate control for health status - reverse causation
- The BMI referent group
- The inability of BMI to capture body compositional changes with ageing
- The length of follow-up

Interpretation of this evidence presents challenges regarding treatment and management of obesity in later life. Furthermore, there was no reference to the health implications of obesity in older persons in the recent WHO report on Ageing and Health (2015) (World Health Organization, 2015). It is therefore crucial to clarify whether older adults who are obese are or are not at a greater risk of mortality and diseases related to adiposity.

This introductory chapter provides an overview on the definition and the prevalence of obesity, body composition changes with advancing age, the techniques available to assess adiposity, and epidemiological studies which have reported on the associations between BMI and health outcomes in younger and middle aged cohorts. Studies reporting on the associations between BMI and mortality in later life will then be summarised and the obesity paradox will be discussed. Additionally, studies reporting associations between BMI and dementia will be reviewed. The data sources used and the overall objective and aims of this thesis will be presented.

1.2. Definition and causes

Obesity has been defined as the "abnormal or excessive fat accumulation that may impair health" (World Health Organization, 2000). Simplistically, this fat accumulation is due to an energy imbalance, in that energy intake has exceeded energy expenditure over an extended time frame (Comptroller and Auditor General, 2001; Bales and Buhr, 2008). The 2007 Foresight report emphasised that the body's ability to balance energy is influenced by our rapidly changing environment; our physiology (including genetic predisposition), eating behaviours, physical activity, and psychosocial impacts were identified as four core areas influencing obesity. The vast array of influences underpins that obesity is a multifactorial disease (Butland *et al.*, 2007).

1.2.1. Body mass index

In clinical practice, body mass index (BMI) is the most widely used metric to assess obesity, with values ≥30 kg/m^2 classifying persons as obese (Willett, Dietz and Colditz, 1999; Bales and Buhr, 2008). BMI is used as a surrogate for adiposity, with a person's weight (kilograms) scaled to their height (metres) squared (Aronne and Segal, 2002; Snijder *et al.*, 2006). BMI is an inexpensive surrogate measure of obesity, requiring only height and weight measurements, enabling population comparisons and trends to be documented globally (Duren *et al.*, 2008).

Table 1.1 shows the WHO definitions for the BMI categories which have been incorporated in the National Institute of Health and Clinical Excellence (NICE) guidelines (World Health Organization, 2000; NICE Guidelines, 2014). These BMI categories were proposed to identify individuals, presently or in the future, at a heightened risk of obesity related conditions (Aronne and Segal, 2002). For the adult population, BMI categories are applied uniformly across the age range and these were primarily derived from epidemiological studies that used younger and middle aged adults (Janssen and Mark, 2007; Mathus-Vliegen, 2012).

Table 1.1 | WHO BMI Classification (World Health Organization, 2000)

Definition	**BMI range kg/m^2**
Underweight	<18.5
Normal weight	18.5-24.9
Overweight	25.0-29.9
Obese	≥*30.0*
Obese-1	30.0-34.9
Obese-2	35.0-39.9
Obese-3	≥40.0

Applicability of the BMI categories across all ethnic groups and age ranges has, however, been questioned (Heiat, Vaccarino and Krumholz, 2001; Rolland *et al.*, 2014; Winter *et al.*, 2014). NICE has recommended for Black African, Black African Caribbean, South Asian, and Chinese populations lower BMI thresholds for indicating increased type 2 diabetes risk (increased risk from BMI 23.0 kg/m^2 and high risk from BMI 27.5 kg/m^2) (NICE Guidelines, 2013, 2014). The applicability of BMI categories for older adults will be discussed further in **section 1.8**.

1.3. Prevalence

Globally in 2014, 266 million men (Credible Interval[1] [CrI] 240, 290 million) and 375 million (CrI 344, 407 million) women were classified as obese using the BMI metric. The global trend data for obesity do not suggest a substantial decline for any country (Di Cesare *et al.*, 2016). In England, the Health Survey for England (HSE) is an annual survey which records the health status and lifestyle factors of adults and children inhabiting private households, and has enabled trend data to be documented since 1993 (NatCen Social Research, 2016). The HSE data for 2015 further highlighted the severity of obesity across the older age range. **Table 1.2** shows the prevalence of adults within each BMI category for the age groups 65 to 74, 75 to 84, ≥85 years by gender. For the youngest age group 29.9% of the females and 32.3% of the males were classified as BMI Obese (BMI ≥30 kg/m^2), and for the oldest age group this was 21.6% and 13.3%, respectively (Health Survey for England, 2017).

[1] Credible interval is equivalent to the uncertainty interval

Table 1.2 | Prevalence of BMI categories by age group for females and males from the Health Survey for England 2015 (Health Survey for England, 2017)

BMI category (kg/m^2)	**Females (%)** *Age group (years)*			**Males (%)** *Age group (years)*		
	65 to 74	75 to 84	≥85	65 to 74	75 to 84	≥85
<18.5	1.0	1.6	0.8	0.2	0.7	1.7
18.5-24.9	33.9	29.1	37.8	22.3	22.7	25.1
25.0-29.9	35.2	39.2	39.8	44.2	51.5	60.0
30.0-39.9	26.4	28.0	20.3	30.3	25.1	13.3
≥40.0	3.5	2.2	1.3	2.0	-	-

It should be noted that the response rate for providing valid height and weight measures for the HSE declined with advancing age. A valid BMI measure was available for 83% of the females aged 65 to 74 years surveyed, and 56% of the females aged ≥85 years surveyed. For males, these figures were 88% and 63% respectively. In the oldest age ranges, refusal of height and weight measures were predominantly due to health conditions which may have affected prevalence estimates (Moody, 2016). Furthermore, the reduced prevalence of obesity in later life may be due to selective survival (Villareal *et al.*, 2005).

1.4. Body composition changes with ageing

Overall, body weight and BMI tend to increase up to the seventh decade of life (Elia, 2001; Villareal *et al.*, 2005; Zamboni *et al.*, 2005; Miller and Wolfe, 2008). Muscle mass tends to decline from the third or fourth decade of life which is paralleled by an increase in fat mass (Villareal *et al.*, 2005) and thereby weight may remain unchanged (Zamboni *et al.*, 2014). Several longitudinal studies have reported on these body composition changes with advancing age. Gallagher *et al.*, (2000) showed there was a decline in the total appendicular skeletal mass with no significant change in body weight for 24 males and 54 females aged 62 to 96 years during a mean follow-up period of 4.7 years (Gallagher *et al.*, 2000). This loss of skeletal mass during ageing is commonly referred to as sarcopenia (Zamboni *et al.*, 2005). Furthermore, Hughes *et al.*, (2004) reported an increase in fat mass but no significant change in body weight for 54 males and an increase in body weight and fat mass for 75 females during a maximum follow-up period of 12 years; participants were aged 46 to 78 years. For both genders, there was a significant decrease in subcutaneous fat mass (Hughes *et al.*, 2004). Similarly, Fantin *et al.,* (2007) documented that there was an increase in fat mass in weight stable (≤ 3% weight loss) adults during a 5.5 year follow-up period; this analysis included 62 males (mean age 71.6 years) and 97 females (mean age 71.4 years). Appendicular and leg fat free mass were reduced during the follow-up (Fantin *et al.*, 2007). There is also an increase in the proportion of fat mass within non-adipose tissues with ageing. Muscular strength can be reduced from the deposition of triglycerides intramuscularly (Ellis, Crowe and Lawrence, 2013).

With ageing, energy expenditure is reduced and there is also a redistribution of fat mass. Energy expenditure is reduced in part due to decreasing metabolic rate, physical activity, and fat oxidation (Elia, 2001; Villareal *et al.*, 2005; Miller and Wolfe, 2008). There is a redistribution of excess fat mass into visceral adipose tissues (VAT) which is paralleled by a decline in subcutaneous fat mass (Zamboni *et al.*, 2005; Miller and Wolfe, 2008). This fat redistribution is not captured using BMI (Zamboni *et al.*, 2005; Snijder *et al.*, 2006; Miller and Wolfe, 2008; Ellis, Crowe and Lawrence, 2013).

A stable BMI may conceal the increase in fat mass and subsequent decrease in fat free mass hence adiposity may be underestimated (Zamboni *et al.*, 2005; Bales and Buhr, 2008). Gallagher *et al*., (1996) showed that the body fat percentage of older persons (>65 to 94 years) was greater than that of younger persons (20 to <35 years) when comparing the same BMI value (Gallagher *et al.*, 1996). Additionally, an overestimation of adiposity may occur due to loss in height from kyphosis and vertebral compression with ageing (Zamboni *et al.*, 2005; Bales and Buhr, 2008). Sorkin, Muller and Andres (1999) reported that BMI values may be inflated by height loss with advancing age; for males this was estimated to be 0.7 kg/m^2 by the eighth decade and 1.4 kg/m^2 by the ninth decade using data from the Baltimore Longitudinal Study of Aging (BLSA). For females, these estimates were 1.6 kg/m^2 by the eighth decade and 2.6 kg/m^2 by the ninth decade (Sorkin, Muller and Andres, 1999).

Batsis *et al* (2016) compared the BMI defined Overweight and Obese ranges to high body fat percentage derived from dual-energy X-ray absorptiometry (DXA) using National Health and Nutrition Examination Surveys (NHANES) 1994-2004 survey data for adults aged ≥60 years (*n* = 4,984) (Batsis *et al.*, 2016). In the age group 60 to 69 years, 85.7% of the males and 80.7% of the females were correctly classified as having a BMI value ≥25 kg/m^2; for adults aged ≥80 years these figures were 65.8% for the males and 70.8% for the females. Furthermore, for those aged 60 to 69 years, 48.1% of the males and 49.0% of the females were correctly classified as obese; for adults aged ≥80 years these figures were 23.9% for the males and 38.4% for the females (Batsis *et al.*, 2016).

1.5. Techniques to assess obesity and other components of body composition

Along with BMI, there is a range of techniques available to assess adiposity and other components of body composition. The chosen techniques to assess adiposity can be influenced by funding, the sample size, and the size limitations of scanners (computerised tomography [CT] and magnetic resonance imaging [MRI]) (Snijder *et al.*, 2006; Duren *et al.*, 2008; National Academies of Sciences, Engineering, and Medicine, 2016; Teigen *et al.*, 2016).

1.5.1. Anthropometric measurements

Anthropometric measures are used to determine the degree of adiposity, body mass, and body dimensions (Duren *et al.*, 2008). Waist circumference, waist-to-hip ratio (WHR), and waist-to-height ratio (WHtR) are used as surrogate measures of abdominal/central obesity (National Academies of Sciences, Engineering, and Medicine, 2016). Yusuf, *et al*., (2005) showed that independently of BMI, waist circumference and WHR were associated with myocardial infarction using a case control study (Yusuf *et al.*, 2005). The WHO has published sex-specific thresholds for waist circumference measures and WHR, which have been defined for metabolic complications (World Health Organization, 2008). Skinfold thickness can be measured using callipers. The skin and the underlying subcutaneous fat thickness is recorded and these measures are incorporated into a pre-chosen formula to derive body fat percentage (Duren *et al.*, 2008; National Academies of Sciences, Engineering, and Medicine, 2016). These measurements can easily be used in epidemiological studies and clinical settings.

1.5.2. Impedance measures

Bioelectrical impedance analysis (BIA) involves measuring the resistance to a low electrical current which is passed through the body, with fat mass acting as an insulator. Using these measures, fat mass and fat free mass estimates can be derived from prediction models (Kyle *et al.*, 2004; Duren *et al.*, 2008; National Academies of Sciences, Engineering, and Medicine, 2016). BIA is beginning to be used on a much larger scale in prospective studies including the UK Biobank (UK Biobank, 2007).

1.5.3. Body density measures

Body density measures include hydrodensitometry (underwater weighing) and air displacement plethysmography and are based on body density assumptions. Comparisons are made between a person's weight in water and a person's weight on land after controlling for lung volume in hydrodensitometry. Persons with a greater proportion of body fat will be more buoyant relative to those with a lower proportion. In air displacement plethysmography, the air pressure inside the chamber with and without the person being assessed is compared. Body density measures are not practical at the population level (Duren *et al.*, 2008).

1.5.4. Imaging techniques

Imaging techniques include DXA, CT and MRI. Bone mineral density, fat mass, and fat free mass can be estimated using DXA which is based on the attenuation of two different energy X-rays, exerting a very low dose of radiation (Duren *et al.*, 2008; National Academies of Sciences, Engineering, and Medicine, 2016). A disadvantage is that subcutaneous adipose tissue and visceral adipose tissue cannot be differentiated. CT scans and MRI scans are considered the most accurate techniques (gold standards) for measuring subcutaneous adipose tissue and visceral adipose tissue (Ness-Abramof and Apovian, 2008; García-Ptacek *et al.*, 2014). CT and MRI scans are not suitable at the population level due to costs, length of assessment, and with CT scans persons are exposed to high radiation doses (Duren *et al.*, 2008; National Academies of Sciences, Engineering, and Medicine, 2016; Teigen *et al.*, 2016).

Suitability of the use of these approaches for measuring obesity in clinical practice and research settings is determined by the strengths and weaknesses associated with each measure and this is presented in supplementary material table S1.1.

1.6. BMI and health outcomes in younger and middle aged cohorts

It has been well established that there is an increased mortality risk for younger and middle aged adults within the BMI Obese range relative to those within the BMI Normal range. Increased mortality risks were reported for males aged 40 to 59 years, without coronary heart disease (CHD), diabetes, or stroke within the BMI Obese range (Relative Risk [RR] 1.42 95% Confidence Interval [CI] 1.07, 1.87) relative to those within the BMI 20.0-21.9 kg/m^2 range during a 15 year follow-up period using the British Regional Heart Study (Wannamethee *et al.*, 1998). Similarly, increased mortality risks were documented for females without cardiovascular disease or cancer and aged 30 to 55 years across the BMI Obese range relative to those within the BMI <21.0 kg/m^2 range, over a 24 year follow-up period using the Nurses' Health Study. Mortality risks were 1.57 (CI 1.44, 1.71) for those within the BMI 30.0-32.9 kg/m^2 range, and 2.89 (CI 2.47, 3.38) for those with a BMI ≥40 kg/m^2 (Hu *et al.*, 2004).

There has been speculation that the increasing prevalence of obesity in the United States of America (US) could lead to gains in life expectancy stagnating (Stewart, Cutler and Rosen, 2009) or even declining (Olshansky *et al.*, 2005). Globally for 2015, a BMI of >25 kg/m^2 was estimated to cause 3.96 million deaths (Uncertainty Interval [UI] 2.73 million, 5.3 million) (Forouzanfar *et al.*, 2016). The Prospective Studies Collaboration (2009) reported a 37% (CI 1.31, 1.42) increased mortality risk per 5 kg/m^2 increment in BMI from BMI 25.0 kg/m^2 for adults aged 35 to 59 years, inclusive of 57 cohorts with the first five years of follow-up excluded and adjustments made for age, sex, smoking status, and study site. For never smokers the mortality risk was increased by 43% (CI 1.32, 1.55) per 5 kg/m^2 increment (Whitlock *et al.*, 2009).

BMI defined obesity has been associated with a range of cardiovascular risk factors. For males within the BMI Obese-1 range there were increased odds for diabetes (Odds Ratio (OR) 11.2 CI 9.3, 13.6), hypertension (OR 2.7 CI 2.4, 3.0), and high cholesterol (OR 1.2 CI 1.1, 1.3) relative to those within the BMI range 18.5-24.9 kg/m^2 during a 10 year follow-up period using the Health Professionals Follow up Study (HPFS) (n = 46,060; mean age 54.5 years). Similarly, for females

within the BMI Obese-1 range, there were increased odds of diabetes (OR 10.0 CI 8.4, 11.8) and hypertension (OR 2.1 CI 1.9, 2.2), but not high cholesterol using the Nurses' Health study (*n* = 77,690; mean age 52.9 years) (Field *et al.*, 2001). Blood glucose, blood pressure and cholesterol have been found to mediate the increased risks with elevated BMI for stroke and coronary heart disease by 76.0% (CI 65.0, 91.0%) and 46.0% (CI 42.0, 50.0%), respectively, from a combined analysis of 97 cohort studies (Lu *et al.*, 2014).

Obesity has been associated with a range of outcomes including asthma, cancer, cardiovascular disease, depression, osteoarthritis and type 2 diabetes. Reported associations from meta-analyses inclusive of younger, middle and older aged cohorts for these health outcomes are presented in the supplementary material text S1.1. Obesity has been reported to be associated with disability and admittance to a nursing home facility. Backholer *et al*., (2012) reported increased odds for impairment in Activities of Daily Living (ADL) of 16% (CI 1.11, 1.21) for persons within the BMI Obese-1 range relative to those within the BMI Normal range, from a meta-analysis of eight cross-sectional studies for adults aged ≥19 years. There were increased odds of impairment in ADL of 76% (CI 1.28, 2.41) for those within the BMI Obese-2 range, from a meta-analysis of five cross sectional studies (Backholer *et al.*, 2012). Persons within the BMI Obese-1 and BMI Obese 2 and 3 combined ranges were shown to be more likely to be admitted to a nursing home facility relative to those within the BMI Normal range, Hazard Ratio (HR) 1.31 (CI 1.07, 1.61) and HR 1.69 (CI 1.22, 2.34), respectively, during a maximum follow-up period of 20 years for white ethnicity adults aged 45 to 75 years (*n* = 5,447) using the NHANES (Zizza *et al.*, 2002).

For older adults, there is conflicting evidence on the impact of the obesity trend for health outcomes, especially mortality and dementia. Researchers have not only questioned the use of the conventional BMI thresholds, which were derived primarily from younger and middle aged adults, but also how to define obesity in later life (Heiat, Vaccarino and Krumholz, 2001; Zamboni *et al.*, 2005; Oreopoulos *et al.*, 2009; Rolland *et al.*, 2014; Winter *et al.*, 2014). The remainder of this chapter will, therefore, focus on the associations between obesity and mortality and dementia for adults aged ≥65 years.

1.7. BMI and mortality in later life

1.7.1. Meta-analyses reporting on BMI defined obesity and mortality

Prior to the start of my PhD (1st April 2014) there had been two published meta-analyses assessing the association between BMI and mortality for adults aged ≥65 years, in terms of reporting relative risks or hazard ratios. During my PhD research, there have been four published meta-analyses (with one being an individual participant meta-analysis). **Table 1.3** documents the time frame, inclusion and exclusion criteria, databases searched, number of studies retained, statistical methods and the reported mortality risk estimates for these meta-analyses.

There is conflicting evidence on the association between mortality risk and BMI measured obesity. Whilst Jansen and Mark (2007) reported elevated mortality risks for those within the BMI Obese-1 range relative to those within the BMI Normal range, Flegal *et al*. (2013) found a stagnation of risks for the BMI ranges Obese-1, Obese-2 and Obese-3 combined, as well as reduced risks for those within the BMI Overweight range relative to the BMI Normal range (Janssen and Mark, 2007; Flegal *et al.*, 2013). Moreover, Janssen and Mark (2007) found reduced mortality risks for those within the BMI Overweight and BMI Obese-1 ranges for analyses which used measured height and weight, had less than ten years of follow-up, and were conducted from 1990 onwards. In contrast, an increased mortality risk was reported for those within the BMI Overweight range for studies which excluded major disease(s) at baseline (RR 1.04 CI 1.01, 1.07). Janssen and Mark (2007) noted that very few analyses used the conventional BMI categories for the BMI Overweight and BMI Obese ranges. The main limitation of the systematic review by Janssen and Mark (2007) is that only one database was interrogated, therefore some analyses may have been missed (Janssen and Mark, 2007). A major criticism of the review by Flegal *et al*., (2013) is the use of a broad reference category as it encompasses current smokers, those with conditions associated with weight loss, and physically active adults (Keith, Fontaine and Allison, 2013; Tobias and Hu, 2013; Willett, Hu and Thun, 2013). Additionally, the baseline examination period, length of follow-up, or ethnic origin of the participants were not considered. Flegal *et al*., (2013) also excluded

a high proportion of large scale cohorts and consortia due to the use of narrower BMI categories (Tobias and Hu, 2013).

Four additional meta-analyses were published during my PhD. The meta-analyses by Winter *et al*., (2014) partly aligns with the BMI mortality risk estimates reported by Flegal. Mortality risks were reduced for those within the BMI Overweight range (HR 0.90 CI 0.87, 0.93), and the risks were not significantly different for those within the BMI Obese-1 range (HR 0.96 CI 0.90, 1.02) or the BMI Obese 2 & 3 ranges (HR 1.18 CI 1.00, 1.39) relative to those within the BMI referent group 21.0-24.9 kg/m^2. However, when a narrower BMI referent group was used, 23.0-23.9 kg/m^2, there were increased mortality risks for those with BMI values exceeding 33.0 kg/m^2. For analyses restricted to never smokers and analyses which had not adjusted for factors along the causal pathway (e.g. diabetes), risks for mortality were increased at BMI values >32.0 kg/m^2 (Winter *et al.*, 2014). Moreover, Aune *et al*., (2016) reported an increased mortality risk of 4% (CI 1.01, 1.07) per 5-unit increment in BMI for never smokers. However, in the non-linear dose response analysis, there was an increased mortality risk below the reference BMI 23 kg/m^2 (Aune *et al.*, 2016). Recently, the Global BMI Mortality Collaboration (2016) reported that the lowest mortality risk was at BMI 24.0 kg/m^2 for never smoking adults aged 70 to 89 years without prevalent chronic disease, and with the first five years of follow-up excluded. For all classes of obesity, there were increased mortality risks relative to those within the BMI Normal range (Di Angelantonio *et al.*, 2016). Additionally, Wang (2015) reported that with advancing age there was a decline in the mortality risks for those within the BMI Obese range. However, this analysis was carried out by one reviewer, only one database was interrogated, and the inclusion and exclusion criteria of the studies were not clearly defined. Studies were required to report on two or more age groups, and therefore some additional studies could have been used within each age category by relaxing this criterion (Wang, 2015).

In **Chapter 3** I report on my meta-analysis for the BMI Overweight and Obese-1 ranges with mortality, therefore, to avoid repetition/ duplication individual studies will be discussed in that chapter.

Table 1.3 | Details on meta-analyses which reported on the BMI and mortality risks for adults aged ≥65 years

First Author, date	Databases searched (time frame)	Inclusion criteria	Studies (#); statistical models	Age (years)	BMI categories	Reported results (95% CI)
Janssen, 2007 (Janssen and Mark, 2007)	PubMed (June 2005)	English language studies with ≥1y follow-up reporting estimates for BMI & mortality for adults aged ≥65 y (subgroup/population). Analyses in figure format only were excluded.	32 (26 analyses for overweight; 28 for obese range); Variance based	≥65	18.5 - 24.9 25.0 - 29.9 30.0 - 34.9	1.00 1.00 (0.97, 1.03) 1.10 (1.06, 1.13)
Flegal, 2013 (Flegal *et al.*, 2013)	Embase & PubMed (30th September 2012)	Prospective studies which used standard BMI categories to report hazard ratios for mortality for general populations.	97 (≥65 y: 33 analyses overweight, 11 obese-1, 11 obese-2 & 3); Random effects	≥65	18.5 - 24.9 25.0 - 29.9 30.0 - 34.9 ≥35.0	1.00 0.90 (0.86, 0.94) 0.87 (0.72 ,1.05) 1.20 (0.94 ,1.52)
Winter, 2014 (Winter *et al.*, 2014)	CINAHL, Cochrane library & MEDLINE (1990 & 2013)	English language prospective studies with ≥5 y of follow-up for community based adults aged ≥65 years reporting HR or RR for BMI & mortality. Baseline smoking had to be documented and at least three BMI categories. Population studies of non-white adults were excluded.	32 (*n* = 197,940) 2-stage random effects	≥65	17.0 - 17.9 18.0 - 18.9 19.0 - 19.9 20.0 - 20.9 21.0 - 21.9 22.0 - 22.9 23.0 - 23.9 24.0 - 24.9 25.0 - 25.9 ...	1.48 (1.42, 1.55) 1.38 (1.33, 1.43) 1.28 (1.24, 1.32) 1.19 (1.17, 1.22) 1.12 (1.10, 1.13) 1.05 (1.05, 1.06) 1.00 0.96 (0.96, 0.97) 0.93 (0.92, 0.94)

First Author, date	Databases searched (time frame)	Inclusion criteria	Studies (#); statistical models	Age (years)	BMI categories	Reported results (95% CI)
continued (Winter et al., 2014)					26.0 - 26.9	0.91 (0.90, 0.92)
					27.0 - 27.9	0.90 (0.88, 0.92)
					28.0 - 28.9	0.91 (0.88, 0.93)
					29.0 - 29.9	0.93 (0.90, 0.96)
					30.0 - 30.9	0.95 (0.91, 0.99)
					31.0 - 31.9	0.98 (0.93, 1.03)
					32.0 - 32.9	1.03 (0.97, 1.09)
					33.0 - 33.9	1.08 (1.00, 1.15)
					34.0 - 34.9	1.13 (1.05, 1.23)
					35.0 - 35.9	1.21 (1.10, 1.33)
					36.0 - 36.9	1.28 (1.16, 1.43)
					37.0 - 37.9	1.36 (1.21, 1.52)
Wang, 2015 (Wang, 2015)	PubMed (15th August 2013)	Studies which reported estimates for BMI & mortality using two or more age groups.	20; random effects	65 to <75	18.5 - 24.9	1.00
					M: ≥30	1.19 (1.05, 1.33)
					F: ≥30	1.21 (1.08, 1.34)
				≥75	18.5 - 24.9	1.00
					M: ≥30	1.02 (0.89, 1.15)
					F: ≥30	1.09 (0.97, 1.22)
Aune, 2016 (Aune *et al.*, 2016)	Embase & PubMed (up to September 23 2015)	English language cohort studies with estimates for ≥ 3 BMI categories & mortality. Patient populations with specific health conditions e.g. diabetes & nursing home based studies were excluded.	230 (6 for never smokers aged ≥65 y); random effects & fractional polynomial models	≥65	Nonlinear dose response	
					16.25	1.73 (1.44, 2.08)
					17.5	1.46 (1.26, 1.69)
					20.0	1.16 (1.07, 1.25)
					…	

First Author, date	Databases searched (time frame)	Inclusion criteria	Studies (#); statistical models	Age (years)	BMI categories	Reported results (95% CI)
continued (Aune et al., 2016)					22.0	1.04 (1.01, 1.07)
					23.0	1.00
					24.0	0.97 (0.95, 1.00)
					25.0	0.96 (0.91, 1.01)
					27.5	0.95 (0.85, 1.08)
					30.0	0.99 (0.82, 1.19)
					32.5	1.05 (0.82, 1.36)
					35.0	1.15 (0.83, 1.59)
					36.5	1.28 (0.87, 1.90)
					40.0	1.45 (0.92, 2.29)
					42.5	1.66 (0.98, 2.81)
					45.0	1.92 (1.06, 3.48)
					Per 5 unit BMI ↑	1.04 (1.01, 1.07)
The Global BMI Mortality Collaboration, 2016 (Di Angelantonio *et al.*, 2016)	Embase, MEDLINE & Scopus (January 1970 to January 2015)	Included prospective studies (or multi-cohort studies) with ≥100,000 adults with median ≥5y follow up with height and weight measured & mortality (including cause specific mortality). Excluded participants with BMI <15 or BMI ≥60.	239 (189 never smokers, prevalent disease excluded and first 5 y)	70 to 89 (never smokers without pre-existing disease & first 5y excluded)	15.0 - 18.4	1.38 (1.30, 1.46)
					18.5 - 24.9	1.00 (0.98, 1.02)
					25.0 - 29.9	1.00 (0.98, 1.02)
					30.0 - 34.9	1.19 (1.14, 1.23)
					35.0 - 39.9	1.64 (1.48, 1.82)
					40.0 - 59.9	1.75 (1.57, 1.95)

1.7.2. Continuous measures of BMI and mortality

The effect of advancing age on the association between continuous BMI and mortality has been documented by several studies. Adams *et al*., (2006) showed a U-shaped association between BMI and mortality; with advancing age, there was a marginal decline in the mortality risks for those within the BMI Obese range during a 10 year follow-up for adults aged 50 to 71 years (*n* = 527,265) using the NIH-AARP study (Adams *et al.*, 2006). Peter *et al*., (2015) reported that with advancing age the BMI range associated with the lowest mortality risk shifted to higher values for never smokers. For males this was to age 80 years, and the BMI mortality curves attenuated during a median follow-up duration of 18.6 years using the Vorarlberg Health Monitoring and Prevention Program (*n* = 129,904) (Peter *et al.*, 2015).

Several studies have reported on the BMI range associated with the lowest risk for mortality. Flicker *et al*., (2010) documented that the minimum mortality risk for adults aged 70 to 75 years was within the BMI Overweight range, with the nadir at 26.6 kg/m^2 (CI 25.7, 27.5 kg/m^2) for males and at 26.3 kg/m^2 (CI 25.5, 26.9 kg/m^2) for females during a 10 year follow-up period using the Health in Men Study (HIMS) and the Australian Longitudinal Study of Women's Health (ALSWH) (*n* = 4,677 men and *n* = 4,563 women). Mortality risks were increased in the conventional BMI Normal range and BMI Obese range (Flicker *et al.*, 2010). van Ufelen *et al*., (2010) also reported on the risks for females aged 70 to 75 years using the ALSWH but with a longer follow-up duration of 12 years and larger sample size (*n* = 11,553). The association between BMI and mortality was U-shaped with the minimum mortality risk in accordance with the previous study, this being 25.0-27.0 kg/m^2 (van Uffelen *et al.*, 2010). Likewise, mortality risks were reported by de Hollander *et al*., (2012) for adults aged 70 to 75 years (*n* = 1,970) using the Survey in Europe on Nutrition and the Elderly: a concerted action (SENECA) study. Over a maximum follow-up period of 10 years, the nadir of the mortality risk was 27.1 kg/m^2 (CI 24.1, 29.3 kg/m^2) (de Hollander *et al*., 2012 b). An increased mortality risk was found for those with BMI values >31.4 kg/m^2. Moreover, Rolland *et al*., (2014) showed that the association between BMI and mortality was J-shaped for females aged ≥75 years (*n* = 3,793) during a median follow-up period of 17.7 years using the Epidemiologie de l'Osteoporose study.

The minimum mortality risk was at a BMI value 28.6 kg/m^2. Mortality risks were increased from values ≤24.6 kg/m^2 (Rolland *et al.*, 2014). Similarly, Cheng *et al.*, (2016) reported that the lowest risk for mortality was within the BMI range 28.0-30.0 kg/m^2 during a mean follow-up duration of 10.9 years for adults aged 66.8 to 93.9 years (*n* = 4,565 years), from the Geisinger Rural Aging Study (GRAS) (Cheng *et al.*, 2016).

Comparing the literature reporting on the association between BMI and mortality can be difficult due to studies using varying follow-up periods, model adjustments are not uniform, the BMI referent group is not consistent, the number and thresholds for BMI groups are not consistent (some studies will categorise all obese adults while some will subdivide into classes), subgroups chosen, sample size, and age groups (Baumgartner, Heymsfield and Roche, 1995; Zamboni *et al.*, 2005; Teucher, Rohrmann and Kaaks, 2010). Additionally, populations differ in the prevalence of chronic conditions, risk factor exposure, and overall mortality rates. Challenges with epidemiological studies with older adults are documented within **Table 1.4**.

Table 1.4 | Challenges of epidemiological studies with older adults

Challenges	
Participation	Behavioural factors and health status (e.g. prevalent diseases) may differ between those who respond and non-responders. Volunteers may be healthier (Karasu, 2012; Rizzuto and Fratiglioni, 2014).
Selective survival	Adults susceptible to adverse effects of the exposure of interest may have already died (Karasu, 2012; Rizzuto and Fratiglioni, 2014).
Cognitive decline	Older adults may have difficulty comprehending questionnaires, providing accurate information (e.g. height may be recalled from an earlier stage of life), and recalling previous exposures and health conditions (Karasu, 2012; Rizzuto and Fratiglioni, 2014).
Exposure	Reverse causality may affect the exposure. Exposures may be misclassified due to self-report (e.g. adults may be embarrassed to reveal the extent of behavioural factors) (Karasu, 2012; Rizzuto and Fratiglioni, 2014).
Attrition	Older adults are more likely to die during the study period or drop out due to declining health. This could lead to an underestimation of the association between exposures and morbidity (Karasu, 2012; Rizzuto and Fratiglioni, 2014).

1.8. The obesity paradox

As discussed early an increased mortality risk for those within the BMI Obese range relative to those within the BMI Normal range has been established for younger and middle aged cohorts. In later life, those within the BMI Obese range have reportedly reduced or similar mortality risks relative to those within the BMI Normal range. This opposing mortality risk for the BMI Obese range has been termed the obesity paradox (Bales and Buhr, 2008; Oreopoulos *et al.*, 2009; Dorner and Rieder, 2012; Mathus-Vliegen, 2012; Cetin and Nasr, 2014; García-Ptacek *et al.*, 2014; Dixon *et al.*, 2015). This has led to further debate regarding the optimal BMI range for longevity in later life (Al Snih *et al.*, 2007; Bales and Buhr, 2009).

Some researchers have argued that there should be a major revision of the BMI thresholds, and claim that the obesity paradox is not a paradox but rather the result of an upwards shift for the BMI range associated with the lowest mortality risk with advancing age (Dixon *et al.*, 2015). Additionally, Bales and Buhr (2009) and Fontana and Hu (2014) have emphasised that these paradoxical BMI mortality findings are in discordance with longevity expansion documented in non-humans following dietary restriction (Bales and Buhr, 2009; Fontana and Hu, 2014).

Concerns have been raised on the health implications of the obesity paradox, as health care treatment and management of older persons with obesity will be determined by the interpretation of the evidence (Al Snih *et al.*, 2007; Heymsfield and Cefalu, 2013; Cetin and Nasr, 2014). There is apprehension that this could undermine and reduce momentum in public health interventions aimed at preventing and treating obesity (Stevens *et al.*, 2015). However, if persons with obesity in later life are at a reduced mortality risk, treatment may, therefore, provide no benefit, and perhaps cause harm (Cetin and Nasr, 2014). **Table 1.5** details some of the main methodological and biological explanations for the 'obesity paradox'. This will be followed by a discussion of epidemiological studies which have assessed some of these proposed explanations.

Table 1.5 | Methodological and biological explanations for the obesity paradox

Explanations	
Adjustment for intermediate mediators	Mortality risk estimates may be biased if adjustment is made for intermediates (e.g. diabetes and hypertension) as these are within the causal pathway linking obesity to mortality (Manson *et al.*, 1995; Willett, Dietz and Colditz, 1999).
Cohort effect	The BMI and mortality risk estimates may vary for different cohorts due to different lifestyle factors, environmental factors and characteristics (Seidell and Visscher, 2000; Elia, 2001; Zamboni *et al.*, 2005; Oreopoulos *et al.*, 2009).
Competing risk factors	The number of competing risk factors accumulates with advancing age thereby the effect of BMI on health outcomes may be attenuated (Janssen and Mark, 2007; Teucher, Rohrmann and Kaaks, 2010).
Higher BMI values exerts a protective effect	A higher BMI may provide metabolic reserves during acute illness (Berraho *et al.*, 2010; Fontana and Hu, 2014; Rizzuto and Fratiglioni, 2014). Weight loss may be tolerated to a greater extent in persons with higher BMI values (Al Snih *et al.*, 2007). Additionally, the risk of fracture may be reduced with higher BMI values due to a greater proportion of bone mineral density (Heymsfield and Cefalu, 2013; Cheng *et al.*, 2016).
Length of follow-up	Studies with shorter follow-up durations are less likely to report a positive association between BMI and mortality for persons within the BMI Obese range (Oreopoulos *et al.*, 2009; Mathus-Vliegen, 2012; Rizzuto and Fratiglioni, 2014).
Life expectancy	Life expectancy declines with advancing age. Obesity related diseases/conditions take years to develop, and people may, therefore, die of non-obesity related causes (Seidell and Visscher, 2000; Elia, 2001; Zamboni *et al.*, 2005; Oreopoulos *et al.*, 2009; Mathus-Vliegen, 2012).

Table 1.5 continued

Physical activity and cardiorespiratory fitness	These may confound or modify the relationship between BMI and mortality (Teucher, Rohrmann and Kaaks, 2010; Yerrakalva, Mullis and Mant, 2015).
Reverse causality	Chronic disease or undiagnosed disease, which are associated with an increased mortality risk, can result in weight loss thereby lowering a person's BMI value (Willett, Dietz and Colditz, 1999; Kvamme *et al.*, 2012; Tobias and Hu, 2013; Fontana and Hu, 2014). Following a diagnosis (e.g. diabetes), a person may consciously attempt to lose weight. With advancing age, the likelihood of reverse causality contributing to the obesity paradox increases (Tobias and Hu, 2013; Fontana and Hu, 2014). This can be minimised by excluding persons with weight loss associated diseases, reported weight loss, and excluding early follow-up to account for undiagnosed disease (as deaths during the initial follow-up period are likely to be due to pre-clinical disease) (Willett, Dietz and Colditz, 1999; Adams *et al.*, 2006; Fontana and Hu, 2014).
Risk measures	Stevens *et al*., (1998) and Calle *et al*., (1999) highlighted from analyses of the Cancer Prevention Study I and Study II that with advancing age there is a decline in the relative risk for the associations between BMI and mortality, although the absolute mortality rates are much higher in the oldest age group relative to the youngest (Stevens *et al.*, 1998; Calle *et al.*, 1999)**.**
Selective survival	Persons may have already died at a younger age from obesity related diseases or conditions, thereby survivors may be "resistant" to the effects of obesity (Elia, 2001; Zamboni *et al.*, 2005; Oreopoulos *et al.*, 2009; Mathus-Vliegen, 2012; Fontana and Hu, 2014).

Table 1.5 continued

Smoking	Smoking is associated with an elevated mortality risk and also with lower weight thereby a decreased BMI (Willett, Dietz and Colditz, 1999; Chiolero *et al.*, 2008). BMI mortality risk estimates can, therefore, be distorted with the inclusion of smokers. There will be variability in the intensity and the extent of cigarette smoking (Tobias and Hu, 2013). For older adults, the health implications of smoking are likely to be accentuated compared to younger adults due to a longer exposure to cigarette smoking (Stevens, 2000). Therefore, adjusting for smoking status has been considered inadequate. Residual bias can be minimised by excluding smokers (Willett, Dietz and Colditz, 1999; Tobias and Hu, 2013; Fontana and Hu, 2014).
The BMI referent group	The conventional BMI Normal range in later life will comprise of persons who have always been within this range and physically active, smokers, and those who previously were in the BMI Overweight or Obese ranges but are at a lower BMI due to weight loss associated conditions. The combining of these different groups may elevate the mortality risk for the conventional BMI Normal range and thereby distort mortality risk estimates for higher BMI values (Willett, Dietz and Colditz, 1999; Heymsfield and Cefalu, 2013; Tobias and Hu, 2013; Fontana and Hu, 2014). Approaches have included modelling BMI continuously to determine the BMI range associated with the lowest mortality risk (de Hollander *et al.*, 2012 b; Cheng *et al.*, 2016). Persons within the BMI Normal range could additionally be centrally obese. This is not captured by BMI and could lead to distorted mortality risk estimates for higher BMI values as persons who are centrally obese have been shown to have increased mortality risks.

Table 1.5 continued

The inability of BMI to capture body compositional changes with ageing	Body compositional changes with advancing age can lead to both an underestimation of BMI due to increased fat mass, but also an overestimation of BMI due to height loss (Zamboni *et al.*, 2005; Bales and Buhr, 2008). Allison *et al.*, (1997) highlighted that the use of BMI may conceal the contributions of fat mass and fat free mass to mortality, and recommended the use of body composition measures in future analyses (Allison et al., 1997). Additionally, BMI does not measure fat distribution. With ageing fat is redistributed to a centralised position, and accounting for this body change may be of greater importance in later life (Zamboni *et al.*, 2005; Miller and Wolfe, 2008).
Treatment	Treatment of hypertension, cholesterol, and diabetes, which are associated with obesity, may have led to the mortality risk estimates for persons with obesity lessening (Zamboni *et al.*, 2005; Keith, Fontaine and Allison, 2013; Holme and Tonstad, 2015). Persons within the BMI Overweight and Obese ranges may be more likely to be monitored, to receive medical treatment, and present earlier to health care practitioners (Mehta and Chang, 2011; Heymsfield and Cefalu, 2013; Holme and Tonstad, 2015). Additionally, public health interventions aimed at the general population (e.g. Change for Life) and specific patient populations may have attenuated the mortality risks (Holme and Tonstad, 2015). Thus, these lifestyle and medical treatments would not have been encompassed in studies with earlier baseline periods (e.g. pre 1990s) (Heymsfield and Cefalu, 2013; Holme and Tonstad, 2015).

1.8.1. Explanations for the obesity paradox

BMI referent group

Increased mortality risks have been documented for those within the conventional BMI Normal range. As discussed earlier, Rolland *et al*., (2014) showed there were increased mortality risks for females with BMI values ≤24.6 kg/m^2 and aged ≥75 years (Rolland *et al*., 2014). Likewise, Winter *et al*., (2014) reported there were increased mortality risks for those with BMI values <23.0 kg/m^2 relative to those within the BMI range 23.0-23.9 kg/m^2 for adults aged ≥65 years (Winter *et al*., 2014). Additionally, de Hollander *et al*., (2012) highlighted that using BMI categories may conceal BMI associations with mortality. There were no significant associations between BMI categories and mortality. However, when BMI was assessed continuously there were significant associations with mortality, with an increased risk reported for BMI values >31.4 kg/m^2 (de Hollander *et al*., 2012 b).

Several studies have reported on the association between continuous measures of BMI and mortality to investigate whether the lowest mortality risk lies at the boundary of the current BMI thresholds. These continuous associations were discussed previously in **section 1.7.2.** The BMI range associated with the lowest mortality risk tended to be within the BMI Overweight range (Flicker *et al.*, 2010; van Uffelen *et al.*, 2010; Rolland *et al.*, 2014; Cheng *et al.*, 2016). In contrast, the Prospective Studies Collaboration (2009) reported that the lowest mortality risk was within the BMI range 22.5-25.0 kg/m^2 for all age groups, inclusive of 57 cohort studies (Whitlock *et al.*, 2009). Associations between continuous measures of BMI will be discussed further in **Chapter 5**.

Body compositional changes

Sarcopenia

BMI is a measure of the combination of fat mass and fat free mass. Allison, *et al*., (1997) documented that fat mass and fat free mass have opposing effects on mortality, with fat mass increasing the risk, thus potentially limiting the use of BMI in the elderly (Allison *et al*., 1997). As highlighted in section 1.4, with ageing there is a decrease in fat free mass and muscle mass which is paralleled by an increase

in fat mass and thereby weight and thus BMI may remain unchanged (Villareal *et al.*, 2005; Zamboni *et al.*, 2014). The age-associated loss of skeletal muscle mass and function is referred to as sarcopenia (Zamboni *et al.*, 2005). Brown, *et al.*, (2016) reported that for adults aged ≥60 years (*n* = 4,425), sarcopenia was associated with an increased mortality risk of 29% (95% CI 1.13, 1.47) over a median follow-up period of 14.4 years using data from NHANES III. Participants were classified with sarcopenia if they had low muscle mass (skeletal mass index <10.76 kg/m^2 for men and <6.75 kg/m^2 for women) combined with low gait speed (gait speed ≤0.8m/s) (Brown, *et al.*, 2016). Similarly, Hirani, et al., (2015) reported an increased mortality risk for males aged ≥70 years (*n* = 1,705) who were classified as having sarcopenia, with a 69% increased risk in the fully adjusted model (95% CI 1.17, 2.44) over a median follow-up period of 7.0 years using data from Concord Health and Ageing in Men Project (CHAMP). Sarcopenia was defined as both low appendicular lean mass (<19.75 kg) and low gait speed (≤0.8 m/s) (Hirani, *et al.*, 2015). At present there is, however, no universal agreement on the thresholds for defining sarcopenia (Wannamethee and Atkins, 2015). Therefore, the inability for BMI to account for the age-related changes with body composition could contribute to the paradoxical associations reported in later life.

Central adiposity

As highlighted in **section 1.4**, with ageing fat mass is redistributed into visceral adipose tissues (VAT) which is paralleled by a decline in subcutaneous fat mass which BMI is not able to capture (Zamboni *et al.*, 2005; Snijder *et al.*, 2006; Miller and Wolfe, 2008; Ellis, Crowe and Lawrence, 2013). Persons with central obesity, even within the BMI Normal range, have been shown to have increased mortality risks (de Hollander *et al.*, 2012 a). The use of other measures will be discussed in greater detail within the remainder of this chapter, **Chapter 7** and **Chapter 8**.

Length of the follow-up period

As highlighted earlier, Janssen and Mark (2007) reported there were reduced mortality risks for those within the BMI Obese-1 range (RR 0.78 CI 0.72, 0.84) relative to those within the BMI Normal range for studies which had a follow-up period <10 years with 13 analyses meta-analysed. In contrast, there were increased mortality risks for those within the BMI Obese-1 range (RR 1.22 CI

1.17, 1.28) for studies which had a follow-up period of ≥10 years with 11 analyses meta-analysed (Janssen and Mark, 2007).

Confounding by smoking

Corrada *et al*., (2006) reported that for never and former smokers there was an increased mortality risk for persons within the BMI Obese range relative to those within the conventional BMI Normal range during a maximum follow-up period of 23 years (3% of the sample were aged <65 years). For current smokers, there was no increased mortality risk for those within the BMI Obese range relative to those within the conventional BMI Normal range (Corrada *et al.*, 2006). Similarly, Adams *et al*., (2006) showed that the magnitude of the association between obesity and mortality during a 10 year follow-up was stronger for never smokers compared to former or current smokers for adults aged 50 to 71 years (*n* = 527,265) using the NIH-AARP study. The authors analysed associations between BMI and mortality for never smokers without prevalent disease (cancer, emphysema, end-stage renal disease, heart disease and stroke) across narrower age groups, however, these results were not presented (Adams *et al.*, 2006). Dolan *et al*., (2007) documented that there were reduced mortality risks for women within the second, third, and fourth quintile of BMI relative to those within the first quintile during 8 years of follow-up for women aged ≥67 years (*n* = 8,029) using the Study of Osteoporotic Fractures. Those within the fifth BMI quintile were not significantly different to those within the first quintile for mortality. All the quintiles became not significantly different to those within the first quintile for mortality when the analysis was restricted to never smokers (Dolan *et al.*, 2007). de Hollander et al., (2012) reported that the BMI range associated with the lowest mortality risk was shifted to the left when the analyses was restricted to never smokers for adults aged 70 to 75 years using the SENECA study (de Hollander *et al*., 2012 b).

Confounding by chronic disease

van Uffelen *et al*., (2010) documented that the shape of the mortality risk curve and the minimum mortality BMI range were little changed after the exclusion of women with a history of cancer. A U-shaped relationship was shown and the

minimum mortality risk was found within the range 25.0–27.0 kg/m^2 for women aged 70 to 75 using the ALSWH (van Uffelen *et al.*, 2010).

Confounding by smoking and pre-existing diseases

Al Snih *et al.*, (2007) found that excluding current smokers plus those who died during the first two years of follow-up did not markedly alter the BMI and mortality associations for those aged ≥65 years from 5 sites of the Established Populations for Epidemiologic Studies of the Elderly (EPESE) with a maximum follow-up period of seven years (*n* = 12,725). Those with a BMI of 25.1 kg/m^2 (CI 23.6, 26.6 kg/m^2) had the lowest mortality risk (Al Snih *et al.*, 2007). Flicker *et al.*, (2010) also reported that the minimum mortality risk for adults aged 70 to 75 years was little changed when the analysis was restricted to a healthier subset (exclusion of smokers and those with a history of chronic respiratory illness, diabetes, heart disease, hypertension, or stroke) with the minimum mortality risk remaining within the BMI Overweight range during a 10 year follow-up period using the HIMS and ALSWH studies (Flicker *et al.*, 2010). Conversely, Berrington de Gonzalez *et al.*, (2010) found a U-shaped association between BMI and mortality during a median follow-up duration of 10 years for adults aged 19 to 84 years using data from 19 prospective cohorts. Exclusion of current and former smokers, and subsequently those with heart disease or cancer, resulted in higher mortality risks associated with BMI values of ≥25 kg/m^2 and a J-shaped association (Berrington de Gonzalez *et al.*, 2010). Furthermore, Cheng *et al.*, (2016) reported reduced mortality risks from the fully adjusted model, for those within the BMI Overweight range HR 0.80 (CI 0.71, 0.90) and the BMI Obese-1 range HR 0.78 (CI 0.69, 0.89) relative to those within the conventional BMI Normal range during a mean follow-up duration of 10.9 years for adults aged 66.8 to 93.9 years (*n* = 4,565) using the GRAS. Restricting the analyses to never smokers without prevalent disease at baseline (Charlson index), or to never smokers with the first two or five years of follow-up excluded, shifted the mortality risk estimates to be non-significant for both the BMI Overweight and BMI Obese ranges relative to those within the conventional BMI Normal range (Cheng *et al.*, 2016).

Exclusion of early deaths

Allison *et al*., (1999) reported that the effect of excluding deaths was significant but there was little change in the magnitude of the association between BMI and mortality from a meta-analysis of 29 studies. Assessing the mortality risks by smoking status did not markedly change the results. There were also no significant age associations. The range of years excluded was 1 to 10 years, with an overall mean of 3.78 years. The age range was 14 to 100 years, with an overall mean age of 52.24 years (Allison *et al*., 1999). Berraho *et al*., (2010) documented that the BMI mortality risk estimates were not markedly changed after excluding deaths during the first three years of follow-up for adults aged ≥65 years (n = 3,646) during a maximum follow-up period of 13 years using the PAQUID cohort study (Berraho *et al*., 2010). Mortality risks were not significantly different for those within the BMI Overweight and BMI Obese-1 range relative to those within the BMI range 22.0-24.9 kg/m2. Similarly, Flicker *et al*., (2010) reported that the minimum mortality risk for adults aged 70 to 75 years was little changed when the analysis excluded those who died within the first, second, or third year of follow-up, remaining within the BMI Overweight range using the ALSWH and HIMS studies (Flicker *et al*., 2010). van Uffelen *et al*., (2010) also used the ALSWH and showed that the shape of the mortality risk curve and the minimum mortality BMI range were little changed after the exclusion of the first five years of follow-up with a U-shaped relationship and the minimum mortality risk within the range 25.0–27.0 kg/m2 for women aged 70 to 75 years (van Uffelen *et al*., 2010).

Physical activity and cardiorespiratory fitness

The “fit but fat” theory was coined after some research findings showed that persons within the BMI Obese range combined with good fitness levels had survival advantages compared to those who were thin combined with poor fitness levels. Yerrakalva, Mullis and Mant (2015) reported from their systematic review that 14 out of 15 studies showed that the inverse associations between BMI and mortality remained after further adjustment for physical activity or cardiorespiratory fitness for adults aged ≥60 years. However, only two studies out of all the analyses adjusting for physical activity used a validated physical activity questionnaire, and thus the poor measure of physical activity could

contribute to paradoxical findings. The authors commented that more studies are required using cardiorespiratory fitness rather than a poor physical activity measure (Yerrakalva, Mullis and Mant, 2015).

Use of other measures to assess obesity and components of body composition

The prognostic value of other adiposity measures such as circumference measures (e.g. waist, waist-to-hip and waist-to-height), and body fat measures (e.g. body fat percentage and fat mass) has been examined in the literature. Furthermore, some studies have estimated the associations between measures of fat free mass and health outcomes. These approaches have assessed individual and combined measures (either through cross classification or adjustment for other measures) with health outcomes in later life. Comparisons between these measures have included examining the risk estimates per one standard deviation increment, deriving the area under the receiver operator curve, and comparing category risk estimates (e.g. quintiles).

There have been two systematic reviews on the use of other measures to assess obesity and components of body composition. Chang *et al*., (2012) reported there was no consistency on which of the body fat distribution measures is associated with the strongest mortality risk from a systematic review of 17 studies, with most inclusive of adults aged ≥65 years (Chang *et al.*, 2012). Carmineke *et al*., (2013) reported that measures of abdominal adiposity provide additional risk information independently of BMI and both measures could be utilized in general practice for risk stratification from a systematic review of 18 prospective cohort studies (6 studies were inclusive of adults aged ≥65 years) (Carmienke *et al.*, 2013). Chang *et al*., (2012) and Carmineke *et al*., (2013) highlighted that comparisons between studies can be difficult due to the choice and number of covariates incorporated into statistical models, the age range chosen (risks may differ between the youngest and oldest old), the methods used to assess body composition (e.g. BIA or DXA), categorization of anthropometric measures, and any chosen exclusion criteria (Chang *et al.*, 2012; Carmienke *et al.*, 2013).

de Hollander *et al*., (2012) reported on the joint associations of BMI and waist circumference measures from a meta-analysis of 29 cohorts (*n* = 58,000). The following groups were used for the waist circumference measures; small (<94 cm for males and <80cm for females) and large (≥102 cm for males and ≥88cm for females). For adults aged 65 to 74 years, there were elevated mortality risks during the five year follow-up period across the BMI categories for those with a large waist relative to those with a BMI within the range 20.0-24.9 kg/m^2 combined with a small waist, with adjustments made for age and smoking. Males and females within the BMI range 20.0-24.9 kg/m^2 combined with a large waist had an increased mortality risk (males RR 1.7 CI 1.2, 2.2; females RR 1.7 CI 1.3, 2.3). Similarly, for those within the BMI Overweight range combined with large waist there were increased mortality risks (males RR 1.1 CI 1.0, 1.3; females RR 1.4 CI 1.1, 1.7). Likewise, for those within the BMI Obese range combined with large waist there were increased mortality risks (males RR 1.1 CI 1.0, 1.3; females RR 1.6 CI 1.3, 1.9). Analyses restricted to never smokers, exclusion of those with major prevalent disease, exclusion of deaths within the first two years, or narrower age groups (65 to 69 years and 70 to 74 years) did not significantly alter the results for mortality. However, this review had a response rate of 28 out of 100 contacted investigators collaborating to the meta-analysis (de Hollander *et al*., 2012 a).

Additional studies which have reported on mortality risks for other adiposity measures and components of body composition will be discussed in **Chapters 7** and **8** to avoid repetition.

1.9. Obesity and dementia

Paradoxical BMI risks have been shown for dementia. In midlife, those within the BMI Obese range have been reported to be at an increased risk for dementia relative to those within the BMI Normal range (Kivipelto *et al.*, 2005; Whitmer *et al.*, 2005). Pedditzi *et al*., (2016) reported an increased risk for dementia of 41% (CI 1.20, 1.66) for those within the BMI Obese range relative to those within the BMI Normal range, from a meta-analysis of four studies which had a mean participant age <65 years. However, there were reduced risks for dementia of 17% (CI 0.74, 0.94) for those within the BMI Obese range relative to those within the BMI Normal range from a meta-analysis of four studies with a mean participant age of ≥65 years. There was no significant difference between those within the BMI Overweight range (RR 0.88 CI 0.76, 1.02) relative to those within the BMI Normal range for dementia from a meta-analysis of five studies. Additionally, the authors reported that six studies had used a continuous measure for BMI for those within the BMI Obese range with one positive, two inverse, and three non-significant associations for dementia. For the overweight range, three showed inverse associations and four non-significant associations (Pedditizi, Peters and Beckett, 2016; Pedditzi, Peters and Beckett, 2016). In a previous meta-analysis by Xu *et al*., (2015) estimates were also reported for the association between high BMI and dementia. However, the included studies differed on their definition of a high BMI and the BMI control category was not clearly defined (Xu *et al.*, 2015).

Individual studies

Epidemiological studies which have reported on the associations between BMI and dementia for adults aged ≥65 years published since 1st January 2000 and including over 1,000 adults are summarised in the supplementary material tables S1.2 and S1.3. Comparability, again, between these studies is challenging due to the different age ranges chosen, the length of follow-up, the BMI categories, and model adjustments. None of the studies used a competing risks approach to estimate the association between BMI and incident dementia.

Dementia risks for the BMI Obese range

Equivocal risks have been reported for the association between the BMI Obese range and incident dementia relative to those within the BMI Normal range. An increased risk for incident dementia was reported for those within the BMI Obese range (HR 1.76 CI 1.03, 2.88) relative to those with a BMI <30.0 kg/m^2 over a maximum follow-up period of 5 years for adults aged ≥65 years from the Cache Country Study of Memory Health and Aging (Hayden *et al.*, 2006). In contrast, Fitzpatrick *et al*., (2009) documented reduced risks for incident dementia for those within the BMI Obese range (HR 0.63 CI 0.44, 0.91) relative to those within the BMI range 20.0-25.0 kg/m^2 over a mean follow-up period of 5.4 years for adults aged 65 to 97 years from the Cardiovascular Health Study (CHS) (Fitzpatrick *et al.*, 2009). Power *et al*., (2010) found the risk for incident dementia was not significantly different for those within the BMI Obese range (HR 0.82 CI 0.67, 1.01) relative to those within the BMI 18.5-24.9 kg/m^2 over a maximum follow-up period of 13.4 years for males aged 65 to 84 years using the HIMS (Power *et al.*, 2011). Tolppanen *et al*., (2014) also showed the risk for incident dementia was not significantly different for those within the BMI >30 kg/m^2 range (HR 0.55 CI 0.23, 1.34) relative to those within the BMI <25 kg/m^2 range during the follow-up period for adults aged 65 to 79 years from the Cardiovascular risk factors, Aging and Dementia Study (Tolppanen *et al.*, 2014). Moreover, Wotton and Goldacre (2014) documented the risks for incident dementia differed depending on the age range. The risks for incident dementia were not significantly different for those within the BMI Obese range (RR 0.97 CI 0.93, 1.01) relative to those who were non-obese according to BMI for adults aged 70 to 79 years but was associated with a reduced risk for adults aged ≥80 years (RR 0.78 CI 0.74, 0.82) over a maximum follow-up period of 14 years using a record linkage cohort study (Wotton and Goldacre, 2014). The BMI associations with dementia will be discussed further in **Chapter 6**.

Explanations

The proposed explanations for the reversal of BMI risks with dementia show similarities to those suggested for the reversal of BMI risks with mortality in later life (Luchsinger *et al.*, 2007; Atti *et al.*, 2008; Fitzpatrick *et al.*, 2009; Tolppanen *et al.*, 2014).

These include:

- Attenuation of health risks with advancing age
- Broad age range
- Reverse causation
- Selective survival
- The BMI referent group
- The inability of BMI to capture body compositional changes with ageing

Weight loss has been reported to precede the clinical diagnosis of dementia within the previous decade (Knopman *et al.*, 2007). Therefore, the conventional BMI Normal range may contain persons whose BMI has been reduced due to preclinical stages of dementia and thus risk estimates for higher BMI categories may be distorted.

1.10. Overall summary

There is conflicting evidence on the association between the BMI Obese-1 range and mortality in later life. Moreover, several analyses have shown that those within the BMI Overweight range have the lowest mortality risk. There is equivocal evidence on the association between BMI defined obesity and incident dementia. These mixed results can lead to confusion on how to treat, manage, and convey research evidence to the public. Comparisons between studies are challenging due to different age groups, time frames used, model adjustments, BMI categories, the BMI referent group and the exclusion criteria. Assessing the association between BMI and health outcomes in later life is crucial as this is the predominant metric used to assess obesity. As highlighted in **Table 1.5** there are many proposed contributors to the paradoxical associations in later life. A multiple simultaneous approach is required as BMI mortality risk estimates may be biased if only one contributor (e.g. smoking) is assessed. A limited number of studies have used a multiple simultaneous approach. Thus, there is a need to use large datasets to account concurrently for multiple contributors (e.g. smoking, weight loss associated disease, and the BMI referent group) to the paradox.

1.11. Data sources

In this thesis, I use two English datasets, namely the Clinical Practice Research Datalink (CPRD) and the UK Biobank. These complimentary datasets offer a unique opportunity to provide updated estimates on the health implications of BMI defined obesity using a population-representative dataset (CPRD) and from a volunteer cohort study (UK Biobank). The CPRD is a research service which maintains a large database of de-identified medical health records collated in primary care establishments (CPRD, 2017). For English patients there has been external linkage to Hospital Episode Statistics (HES) and the Office for National Statistics (ONS) (Williams *et al.*, 2012; Herrett *et al.*, 2015; Stevenson, 2015). Due to the large scale of the datasets, stratified analyses accounting for smoking and conditions associated with weight loss, both of which can distort risk estimates, can be achieved whilst maintaining a sufficient sample size to detect statistical associations. The UK Biobank is a prospective cohort study with enrolment of volunteers aged 40 to 69 years initiated in 2006-2010. As with the CPRD there has been external linkage to HES and ONS (Allen *et al.*, 2012;

Sudlow *et al.*, 2015; Trehearne, 2016). This dataset not only allows estimates for health outcomes to be reported for BMI but also for other surrogate measures of adiposity (e.g. waist circumference, WHR, and WHtR) and components of body composition measures (e.g. body fat percentage, and fat mass index) as these were concurrently collected at baseline.

1.12. Thesis objectives

The overall aim of this thesis is, therefore, to clarify whether older persons with obesity are or are not at a greater risk for mortality and for dementia. I will then assess whether persons within the BMI Overweight range have the lowest mortality risk. The associations between BMI and CHD and diabetes will also be estimated. There is great urgency to provide updated risk estimates due to the increasing prevalence of obesity in England in later life. Methodological flaws in the analysis stages of previous studies such as inadequate control for smoking, inclusion of persons with conditions associated with weight loss, and the chosen BMI referent group may have caused these mixed messages regarding the health implications of obesity for mortality and dementia. Assessing the impact of a single contributor (e.g. smoking) to the paradox could still result in flawed BMI mortality risk estimates and thus a multiple simultaneous approach is required. Clinical practice guidelines on managing and treating obesity were not intended to be used for already ill persons. Other adiposity measures and components of body composition will be assessed as BMI is unable to capture the body composition changes with ageing. These will be assessed individually and jointly with BMI.

The **objectives** of this thesis are:

1. To conduct a review and meta-analysis of cohort studies which reported mortality risk estimates for adults aged ≥65 years for the BMI Overweight range and/or BMI Obese-1 range. To determine the influence of specific exclusions (smokers, conditions associated with weight loss, and early follow-up) and combinations of exclusions with consideration of the BMI

referent group for the risk of mortality. This is presented in **Chapter 3.**

2. To estimate the associations between the WHO BMI categories and mortality using a large cohort of population representative patients (aged ≥60 years) – the CPRD – within narrower age bands, and additionally to estimate the associations in subgroups of 'healthier agers' and 'non-healthier agers'. This is presented in **Chapter 4**.

3. To re-define the BMI referent group by estimating the continuous BMI association with mortality, and to use this revised referent group to estimate the associations for mortality, incident coronary heart disease, and type 2 diabetes using the CPRD for adults aged ≥60 years. This is presented in **Chapter 5**.

4. To estimate BMI associations with incident dementia using a revised referent BMI group assessing the impact of short and longer term follow-up with a competing risks approach using the CPRD for adults aged 65 to 74 years. This is presented in Chapter 6.

5. To estimate the associations between the WHO BMI categories and mortality using a large volunteer cohort. Secondly, to compare established measures of body fat distribution and body composition to BMI for mortality prediction for 'healthier agers' within the seventh decade of life and to describe the concordance (percentage agreement) between categories of BMI and these different measures using the UK Biobank. This is presented in **Chapter 7**.

6. To estimate associations between combined measures of BMI and waist-hip ratio with mortality, and incident coronary heart disease using the UK Biobank. This is presented in **Chapter 8**.

An overview of the methods used in this thesis will be provided in **Chapter 2**.

1.13. Publications

During my PhD I have had two first author paper publications. One forms the basis of Chapters 4 and 5.

> Bowman, K., Delgado, J., Henley, W. E., Masoli, J. A., Kos, K., Brayne, C., Thokala, P., Lafortune, L., Kuchel, G. A., Ble, A., & Melzer, D. (2017) Obesity in Older People With and Without Conditions Associated With Weight Loss : Follow-up of 955,000 Primary Care Patients. J Gerontol A Biol Sci Med Sci. Editor's Choice. 72(2): 203–209.

The second manuscript forms the basis of Chapter 8.

> Bowman, K., Atkins, J.L., Delgado, J., Kos, K., Kuchel, G.A., Ble, A., Ferrucci, L., & Melzer, D. (2017) Central adiposity and the overweight risk paradox in aging: follow-up of 130,473 UK Biobank participants. AJCN. 06(1):130-135.

I have submitted Chapter 6 for publication. I have also collaborated on several papers which are presented in the supplementary material text 1.2.

1.14. Structure of thesis

Chapter 1 provides the background to this thesis. An overview on the definition and prevalence of obesity is provided. Epidemiological studies reporting on the association between BMI and health outcomes in younger and middle aged cohorts, and in later life are summarised. Contributors to the 'Obesity paradox' are discussed. The overall aim and objectives are presented. **Chapter 2** describes the data sources (CPRD and UK Biobank) and the statistical techniques used within this thesis. **Chapters 3** to **8** presents the analyses from the six objectives and are structured in the format of a manuscript: summary, introduction, methods, results, discussion and conclusion. **Chapter 9** summarises the research findings from this thesis.

Supplementary material for Chapter 1

List of Tables for supplementary material for Chapter 1

List of Texts for supplementary material for Chapter 1

Table S1.1 | Advantages (✓) and disadvantages (x) to the approaches to assess adiposity and other components of body composition

Approach	✓ Advantages	× Disadvantages
Anthropometric measures		
Body mass index	✓ Most frequently used index ✓ Population and trend comparisons ✓ Inexpensive and non-invasive ✓ Quick and easy to measure ✓ Minimal to zero training required	× Fat mass and fat free mass cannot be differentiated × Surrogate measure of adiposity × Correlation between BMI and fat mass modified with fitness, ethnicity, and age × Does not measure fat distribution
Skinfold thickness	✓ Inexpensive	× Training required × Intraobserver/ interobserver errors × Body contact required × Different methods and formulas
Waist circumference	✓ Inexpensive ✓ One measure ✓ Quick to measure ✓ Suitable for population surveillance	× Subcutaneous adipose tissue and visceral adipose tissue cannot be differentiated × Training required and different protocols × Intraobserver/ interobserver errors

Table S1.1 continued

	✓ Advantages	× Disadvantages
Waist circumference continued		× Body contact required × Proxy for central adiposity × Does not account for body stature
Waist-to-hip ratio/ Waist-to-height ratio	✓ Inexpensive ✓ Adjustment for body shape ✓ Quick to measure ✓ Suitable for population surveillance	× Subcutaneous adipose tissue and visceral adipose tissue cannot be differentiated × Training required and different protocols × Intraobserver/ interobserver errors × Body contact required
Impedance		
Bioelectrical Impedance Analysis (BIA)	✓ Easily measured ✓ Non-invasive ✓ Inexpensive ✓ Portable devices ✓ Quick to measure	× Differences in quality and accuracy of devices × Intraobserver/ interobserver errors

Table S1.1 continued

	✓ Advantages	× Disadvantages
BIA continued		× Readings can be affected by skin conditions, body composition, and fluid volume × Subcutaneous adipose tissue and visceral adipose tissue cannot be differentiated × Some machines may estimate from specific limbs only e.g. arms
Densitometry		
Air displacement plethysmography	✓ Measure of body fat	× Training required × Specialised and expensive equipment × Persons required to wear close fitting bathing suit and cap × Not practical at the population level
Hydrodensitometry (underwater weighing)	✓ Measure of body fat	× Not practical at the population level × Time consuming × Training required

Table S1.1 continued

	✓ Advantages	× Disadvantages
Hydrodensitometry continued		× Requires full body water submersion and for the person to remain still × Specialised and expensive equipment × Measurements can be affected by the humidity and temperature
Imaging		
Computed tomography (CT)	✓ Subcutaneous adipose tissue and visceral adipose tissue measured ✓ Non-adipose tissues can be measured	× High radiation doses × Time consuming × Not practical at the population level × Interpretation of results can be affected by patient alignment and the slice thicknesses × Specialised and expensive equipment
Dual energy X-ray absorptiometry	✓ Bone, fat mass and fat free mass can be estimated ✓ Whole body imaging	× Manufacturer assumptions vary × Machine algorithms vary × Training required

Table S1.1 continued

	✓ Advantages	× Disadvantages
Dual energy X-ray absorptiometry continued		× Subcutaneous adipose tissue and visceral adipose tissue cannot be differentiated × Specialised and expensive equipment
Magnetic resonance imaging (MRI)	✓ Subcutaneous adipose tissue and visceral adipose tissue measured ✓ No radiation exposure	× Specialised and expensive equipment × Not practical at the population level × Time consuming

This table has been based on a number of papers (Kyle *et al.*, 2004; Snijder *et al.*, 2006; Duren *et al.*, 2008; Ness-Abramof and Apovian, 2008; World Health Organization, 2008; National Academies of Sciences, Engineering, 2016; Teigen *et al.*, 2016).

Text S1.1 | Reported associations between BMI and a range of health outcomes from meta-analyses

Cardiovascular outcomes

Wormser *et al*., (2011) reported an increased risk for CHD of 29% (CI 1.22, 1.37) per 4.56 kg/m^2 increment for adults (mean age 58 years) with a BMI ≥20 kg/m^2 using 51 studies. There was an increased risk for ischaemic stroke of 20% (CI 1.12, 1.28) per 4.56 kg/m^2 increment for adults (mean age 58 years) with a BMI ≥20 kg/m^2 using 25 studies. Adjustments were made for age, sex, and smoking (Wormser et al., 2011).

Cancer subtypes

Renehan *et al*., (2008) documented on the relative risks associated with a 5 kg/m^2 increment for a range of cancer subtypes from 141 articles. For males, there was an increased relative risk for the following cancer sites and types: oesophageal adenocarcinoma (RR 1.52 CI 1.33, 1.74), thyroid (RR 1.33 CI 1.04, 1.70), colon (RR 1.24 CI 1.20, 1.28), renal (RR 1.24 CI 1.15, 1.34), malignant melanoma (RR 1.11 CI 1.05, 1.18), multiple myeloma (RR 1.11 CI 1.05, 1.18), rectum (RR 1.09 CI 1.06, 1.12), leukaemia (RR 1.08 CI 1.02, 1.14), and non-Hodgkin lymphoma (RR 1.06 CI 1.03, 1.09). For females, there were increased risks for the following: endometrium (RR 1.59 CI 1.50, 1.68), gallbladder (RR 1.59 CI 1.02, 2.47), oesophageal adenocarcinoma (RR 1.51 CI 1.31, 1.74), renal (RR 1.34 CI 1.25, 1.43), leukaemia (RR 1.17 CI 1.04, 1.32), thyroid (RR 1.14 CI 1.06, 1.23), postmenopausal breast (RR 1.12 CI 1.08, 1.16), pancreas (RR 1.12 CI 1.02, 1.22), multiple myeloma (RR 1.11 CI 1.07, 1.15) and colon (RR 1.09 CI 1.05, 1.13) (Renehan *et al.*, 2007).

Type 2 diabetes

Vazquez *et al*., (2007) showed an increased risk for type 2 diabetes of 87% (CI 1.67, 2.10) per 4.3 kg/m^2 increment for adults aged between 20 and 80 years using 32 studies (Vazquez *et al.*, 2007). Moreover, Guh *et al*., (2009) reported the risks for incident type 2 diabetes separately for males and females. For males aged ≥35 years, there was an increased risk for type 2 diabetes for those within

the BMI Obese range (RR 6.74 CI 5.55, 8.19) relative to those within the BMI Normal range using four studies. For females aged ≥30 years, there was an increased risk for type 2 diabetes for those within the BMI Obese range (RR 12.41 CI 9.03, 17.06), using four studies (Guh *et al.*, 2009).

Depression

Luppino *et al*., (2010) documented an increased odds of depression of 57% (CI 1.23, 2.01) for persons within the BMI Obese range relative to those who were non-obese using four studies (Luppino *et al.*, 2010). Increased odds of depression of 18% (CI 1.01, 1.37) for those within the BMI Obese range relative to those who were non-obese were also reported for adults aged ≥14 years using 17 studies (de Wit *et al.*, 2010). Gariepy, Nitka and Schmitz (2010), found the odds of anxiety disorders were increased by 40% (CI 1.2, 1.6) for persons within the BMI Obese range relative to those who were non-obese for adults aged ≥15 years using 13 studies (Gariepy, Nitka and Schmitz, 2010).

Asthma

Beuther and Sutherland (2007) reported an increased odds of incident asthma after 12 months of follow-up for those within the BMI Obese range (OR 1.92 CI 1.43, 2.59) relative to those within the BMI Normal range using seven studies (Beuther and Sutherland, 2007).

Osteoarthritis and back pain

Guh *et al*., (2009) showed an increased risk for osteoarthritis for males and females within the BMI Obese range (males: RR 4.20 CI 2.76, 6.41; females RR 2.19 CI 1.77, 2.71) relative to those within the BMI Normal range using two studies (Guh *et al.*, 2009). Jiang *et al*., (2011) found an increased risk for hip osteoarthritis per 5-unit increment in BMI (RR 1.11 CI 1.07, 1.16) using 14 studies (Jiang *et al*., 2011). Blagojevic *et al*., (2010) reported increased odds of knee osteoarthritis for those within the BMI Obese range (OR 2.22 CI 1.91, 2.57) relative to those within the BMI Normal range using 12 cohort studies with the participants mean age 50 years (Blagojevic *et al.*, 2010). An increased risk for knee osteoarthritis per 5-unit increment in BMI (RR 1.35 CI 1.21, 1.51) was also

found from a meta-analysis of 21 studies. (Jiang *et al.*, 2012). Shiri *et al.*, (2009) reported increased odds of lower back pain for those within the Obese range (OR 1.33 CI 1.14, 1.54) relative to those within the BMI Normal range, using eight cross sectional studies. This was also the case using five cohort studies, (OR 1.53 CI 1.22, 1.92) (Shiri *et al.*, 2010).

Table S1.2 | Reported associations using Odds Ratios for BMI and dementia for adults aged ≥65 years and ≥1000 subjects

Study; baseline year(s) (Author, year)	**Subjects**	**Follow up; [events]**	**Model adjustments**	**BMI groups [method]**	**Results**
Anhui cohort study 2001-2003 (Chen *et al.*, 2011)	≥65 y 1,307	7.5 y (max) [80 D]	Age, sex, urban-rurality, educational level, main occupation, annual income, smoking habits, painting/playing chess/flower planting/pet, angina, good relation with others, ease in acquiring friends, living with, worrying, hypochondriasis, anything (else) severely upsetting, & horrifying experience	<20.0 20.0 - <23.0 23.0 - <26.0 ≥26.0 [weight measured]	1.00 0.96 (0.47, 2.00) 0.63 (0.30, 1.33) 0.45 (0.20, 1.05)

Table S1.3 | Reported associations using Hazard Ratios or Relative Risks for BMI and dementia for adults aged ≥65 years and ≥1000 subjects

Study; baseline year(s) (Author, year)	Subjects	Follow up; [events]	Model adjustments	BMI groups [method]	Results
The Kungsholmen Project 1987 (Atti *et al.*, 2008)	≥75 y 1,255 (330 M)	3, 6, and 9y [356 D]	Age, sex, education, MMSE score, depressive symptoms, chronic disease & impairment in ADL	Dementia	
				0 to 9 y	
				continuous	0.98 (0.94, 1.00)
				<20.0	0.97 (0.71, 1.34)
				20.0 - 24.9	1.00
				≥25.0	0.75 (0.59, 0.96)
				3 to 9 y	
				continuous	0.96 (0.92, 1.01)
				<20.0	0.91 (0.59, 1.40)
				20.0 - 24.9	1.00
				≥25.0	0.72 (0.52, 1.02)
				6 to 9 y	
				continuous	0.97 (0.91, 1.04)
				< 20.0	0.74 (0.36, 1.53)
				20.0 - 24.9	1.00
				≥25.0	0.66 (0.40, 1.07)
				AD	
				0 to 9 years	
				20.0 - 24.9	1.00
				≥25.0	0.66 (0.50, 0.88)
				….	

Table S1.3 continued

Study; baseline year(s) (Author, year)	Subjects	Follow up; [events]	Model adjustments	BMI groups [method]	Results
Atti, 2008 continued (Atti *et al.*, 2008)				6 to 9 years 20.0 - 24.9 ≥25.0 [measured]	 1.00 0.67 (0.40, 1.15)
CHS, FHS, HRS, 1989–1999; 1990–2010; 1998–2010; (whole period) (Barnes *et al.*, 2014)	≥65 y CHS 2,794, FHS 2,411, HRS 13,889	NR	Age, education, diabetes, stroke, needs help (money/medications), & depressive symptoms	CHS <18.5 FHS <18.5 HRS <18.5 [measured]	2.66 (1.37, 5.18) 6.26 (2.51, 15.61) 1.82 (1.25, 2.64)
Cardiovascular Health Study 1992-1994 (Fitzpatrick *et al.*, 2009)	65-97 y 2,798 (40.9% M)	5.4 y (mean) [480 D; 245 AD; 213 VaD]	Age, race, sex, years of education, C-reactive protein level, interleukin 6 level, hypertension status, DM, CHD, total cholesterol level, ankle-arm index, smoking status & apolipoprotein E ε4 allele	Dementia Continuous <20.0 20.0 – 25.0 >25.0 – 30.0 >30.0 AD continuous <20.0 20.0 – 25.0 >25.0 – 30.0 >30.0 ….	 0.95 (0.92, 0.98) 1.62 (1.02, 2.64) 1.00 0.92 (0.72, 1.18) 0.63 (0.44, 0.91) 0.95 (0.91, 0.99) 1.42 (0.74, 2.70) 1.00 0.74 (0.52,1.05) 0.58 (0.36, 0.96)

Table S1.3 continued

Study; baseline year(s) (Author, year)	**Subjects**	**Follow up; [events]**	**Model adjustments**	**BMI groups [method]**	**Results**
Fitzpatrick, 2009 continued (Fitzpatrick *et al.*, 2009)				VaD Continuous <20.0 20.0 – 25.0 >25.0 – 30.0 >30.0 [measured]	 0.95 (0.91, 0.99) 2.15 (1.11, 4.19) 1.00 1.20 (0.83, 1.76) 0.72 (0.41,1.27)
The Cache County Study of Memory Health and Aging (CCSMHA) 1995 (Hayden *et al.*, 2006)	≥65 y 3,264 (1,363 M & 1,901 F)	5 y (max) [M: 28 AD, 13 VaD and 41 D F: 76 AD, 24 VaD, and D 100]	Age, gender, education, APOE e4 allele, hypertension, high cholesterol, diabetes, stroke, CABG, & MI	Total dementia BMI ≥30.0 AD BMI ≥30.0 VaD BMI ≥30.0 Females AD BMI ≥30.0 VaD BMI ≥30.0 Males AD BMI ≥30.0 VaD BMI ≥30.0 [self-report]	 1.76 (1.03, 2.88) 1.93 (1.05, 3.36) 1.16 (0.37, 3.12) 2.23 (1.09, 4.30) 1.30 (0.32, 4.29) 1.48 (0.41, 4.18) 0.71 (0.04, 4.31)

Table S1.3 continued

Study; baseline year(s) (Author, year)	Subjects	Follow up; [events]	Model adjustments	BMI groups [method]	Results
Kame Project 1992-1994 (Hughes *et al.*, 2009)	≥65 y 1,478 (44.7% M)	7.8 y (mean, SD 0.3) [129 D cases, 71 AD, and 22 VaD]	Age, sex, education, alcohol, smoking, hypertension, hypercholesterolemia, DM, angina pectoris, stroke, TIA, & PA	Dementia Continuous (*n* = 1,294 unaffected and 108 cases)	0.78 (0.42, 1.44)
				AD Continuous (*n* =1,333 unaffected and 59 cases)	0.56 (0.33, 0.97)
				VaD Continuous (*n* =1,351 unaffected and 19 cases) [measured]	0.66 (0.13, 3.36)
Longitudinal study of aging in New York city - Medicare eligible persons 1999-2001 (Luchsinger *et al.*, 2012)	≥65 y 1,431 with BM data	5,734 p-y of follow-up (140 AD)	Sex, age, ethnicity, education, APOE e4 allele, T2D, hypertension, heart disease, non-HDL cholesterol, HDL cholesterol, & stroke	Continuous BMI quartiles Q1 Q2 Q3 Q4 p for trend [not reported]	0.9 (0.7, 1.1) 1.0 0.4 (0.2, 0.7) 0.7 (0.4, 1.2) 0.6 (0.3, 1.1) 0.19

Table S1.3 continued

Study; baseline year(s) (Author, year)	**Subjects**	**Follow up; [events]**	**Model adjustments**	**BMI groups [method]**	**Results**
Italian Longitudinal Study on Aging (ILSA) 1992 (Noale *et al.*, 2013)	65-84 y 1,093 M & 1,408 F	7.8 y (median) [M: 70 D, F: 124 D]	Age, education, glycemia, triglycerides, HF, parkinsonism, severe depressive symptomatology & mild depressive symptomatology	women <24.1 men [nr]	 1.72 (1.02, 2.90) BMI not significant
PAQUID Study (Nourhashémi *et al.*, 2003)	≥65 y 3,557 (57.2% F)	8 y (66 D)	Sex, age, age-sex interaction, educational level, alcohol consumption & tobacco consumption	<21.0 21.0 – 22.0 23.0 – 26.0 ≥27.0 Dementias between 5 & 8y <21.0 21.0 – 22.0 23.0 – 26.0 ≥27.0 Time point 3y BMI <21.0 Time point 5y BMI <21.0 Time point 8 y BMI <21.0 [self-report]	1.48 (1.08, 2.04) 1.07 (0.76, 1.51) 1.00 0.83 (0.59, 1.18) 1.19 (0.72, 1.96) 0.71 (0.40, 1.25) 1.00 0.72 (0.43, 1.20) 1.56 (0.85, 2.86)* 1.24 (0.61, 2.54)* 1.05 (0.51, 2.26)*

Table S1.3 continued

Study; baseline year(s) (Author, year)	Subjects	Follow up; [events]	Model adjustments	BMI groups [method]	Results
Health In Men Study (HIMS) 1996 (Power *et al.*, 2011)	65-84 y 12,047 M BMI <18.5 excluded.	13.4y (max) [1271 D)	Age, marital status, education, alcohol consumption, fat intake from milk, PA, and prevalent DM, dyslipidaemia & CHD	<25.0 25.0 - <30.0 ≥30.0 exclusion of deaths and dementia cases first 2 y <25.0 25.0 - <30.0 ≥30.0 [measured]	1.00 0.82 (0.70, 0.95) 0.82 (0.67,1.01) 1.00 0.82 (0.70, 0.95) 0.84 (0.69, 1.03)
Uppsala Longitudinal Study of Adult (Rönnemaa *et al.*, 2011)	≥70 y 1,174 M	19 y (max) [246 D, 106 AD, 47 VaD]	Age & education	Dementia AD VaD [measured]	1.0 (0.8, 1.1) 0.9 (0.8, 1.1) 1.2 (0.9, 1.6)

Table S1.3 continued

Study; baseline year(s) (Author, year)	Subjects	Follow up; [events]	Model adjustments	BMI groups [method]	Results
Cardiovascular risk factors, Aging and Dementia (CAIDE) study 1998 (Tolppanen *et al.*, 2014)	65-79y 1,262 for Dementia analysis &1256 for Alzheimer's analysis	Up to 2008	Age, gender, *APOE 4*-status, region of residence, smoking status, education, income, DM, cerebro/cardiovascular disease, SBP, & serum total cholesterol	Dementia continuous <25.0 25.0 – 30.0 >30.0 AD Continuous <25.0 25.0 – 30.0 >30.0 [continuous]	 0.94 (0.86, 1.03) 1.00 0.51 (0.25, 1.04) 0.55 (0.23,1.34) 0.89 (0.81, 0.98) 1.00 0.57 (0.27, 1.19) 0.40 (0.15, 1.08)
THIN database (377 practices) Jan 2000- Dec 31, 2011 (Walters *et al.*, 2016)	80-95 y 130,382	5 y [7,104 D]	Age, age^2, gender, calendar year, current anti-hypertensive use, SBP, lipid ratio smoking status, history of alcohol problem, DM, AF, current anxiety/use of anxiolytics, current NSAID use, & current aspirin use	BMI per unit increase	0.95 (0.94, 0.96)

Table S1.3 continued

Study; baseline year(s) (Author, year)	Subjects	Follow up; [events]	Model adjustments	BMI groups [method]	Results
Record linkage cohort study – NHS admission and ONS in England 1999-2011 (Wotton and Goldacre, 2014)	70-79y 75,213 obese & 753,130 controls Aged ≥80 23,423 obese & 46,840 controls)	14 y (max) [70-79 y: 2215 D, 424 AD, 758 VaD OB cohort: 80+ 1513 D, 248 AD, 438 VaD OB cohort]	Sex, age bands, single calendar years, region of residence & deprivation score associated with patients' area of residence in quintiles	70 to 79 y D obese v non-obese	0.97 (0.93, 1.01)
				AD obese v non-obese	0.60 (0.54, 0.66)
				VaD obese vs non-obese	1.07 (0.99, 1.15)
				≥80 y D obese v non-obese	0.78 (0.74, 0.82)
				AD obese v non-obese	0.51 (0.45, 0.58)
				VaD obese vs non-obese	0.81 0.74, 0.89)

* Note these are Odds Ratios

For terms which have been abbreviated see List of abbreviations Table. For studies which have been abbreviated see List of study abbreviations

Text S1.2 | Contributions to accepted publications

1. Delgado J, Bowman K., Ble A, Masoli J, Han Y, Henley W, Welsh S, Kuchel GA, Ferrucci L, Melzer D. Blood pressure trajectories in the 20 years before death: repeat clinical measures in 46,634 individuals. JAMA Internal Medicine [Accepted 20th September 2017]

2. Delgado J, Masoli J, **Bowman K,** Strain D, Kuchel G, Walters K, Lafortune L, Brayne C, Melzer D, Ble A. Outcomes of treated hypertensions in 79,376 patients aged 80 years and older. Linked records based cohort analysis. J Am Geriatr Soc 2016 doi: 10.1111/jgs.14712. [Epub ahead of print]

3. Ble A, Hughes PM, Delgado J, Masoli JA, **Bowman K,** Zirk-Sadowski J, Mujica Mota RE, Henley WE, Melzer D. Safety and Effectiveness of Statins for Prevention of Recurrent Myocardial Infarction in 12 156 Typical Older Patients: A Quasi-Experimental Study. J Gerontol A Biol Sci Med Sci. 2016 May 4. pii: glw082. [Epub ahead of print] PMID: 27146371

4. Pilling LC, Atkins JL, **Bowman K,** Jones SE, Tyrrell J, Beaumont RN, Ruth KS, Tuke MA, Yaghootkar H, Wood AR, Freathy RM, Murray A, Weedon MN, Xue L, Lunetta K, Murabito JM, Harries LW, Robine JM, Brayne C, Kuchel GA, Ferrucci L, Frayling TM, Melzer D. Human longevity is influenced by many genetic variants: evidence from 75,000 UK Biobank participants. *Aging (Albany NY)*. 2016 Mar;8(3):547-60. PMID: 27015805

5. Chan KY, Yu XW, Lu JP, Demaio AR, **Bowman K**, Theodoratou E. Causes of accidental childhood deaths in China in 2010: A systematic review and analysis. *Journal of Global Health*. 2015 Jun;5(1):010412. doi: 10.7189/jogh.05.010412. PMID: 26110052

Chapter 2 Methods

Table of Contents

List of Tables for Chapter 2

List of Figures for Chapter 2

2.1. Summary

This chapter provides an overview of the datasets used in this thesis, namely the UK Clinical Practice Research Datalink (CPRD) and the UK Biobank. The strengths, challenges, and suitability of these datasets, as well as a description of the statistical analyses used and their appropriateness for addressing the research objectives set in **Chapter 1,** will be discussed.

The CPRD and the UK Biobank were chosen as the datasets to analyse for this thesis as both are large scale, provide recent, 1st January 2000 onwards, BMI measures for older adults and offer high quality UK data. The two datasets are complimentary as the CPRD is a population representative dataset and the UK Biobank is a volunteer prospective cohort study. Both datasets allow stratified analyses (e.g. by smoking status and health status) whilst maintaining a sufficient sample size to detect statistical associations.

2.2. Overview of the UK Clinical Practice Research Datalink (CPRD)

The UK Clinical Practice Research Datalink (CPRD) is a research service which operates to maintain a large electronic health database of de-identified medical records collated in primary care establishments (CPRD, 2017). Initiated in April 2012 and financially supported by the NHS National Institute for Health Research (NIHR) and the Medicines and Healthcare Projects Regulatory Agency (MHRA), the CPRD is an expansion of the General Practice Research Database (GPRD); this former database incorporated the Value Added Medical Products (VAMP) dataset which was founded in 1987 (Herrett *et al.*, 2015; CPRD, 2017). The overarching aim of the CPRD is to facilitate researchers with access to de-identified health and social care datasets for observational research which may lead to enhanced public health care (Herrett *et al.*, 2015; Stevenson, 2015). Since the commencement of this research service, advances in drug safety have been made and research findings have steered health guidelines. One of the major advantages with the CPRD is that multiple datasets can be linked e.g. primary and secondary care.

2.2.1. National Health Service

In the UK, universal healthcare is provided by the National Health Service (NHS) without cost being incurred to patients for appointments or hospital admissions and treatment (prescriptions, however, may involve payment). More than 98% of the UK population are registered with a general practitioner (GP) for primary care with each patient having a specific NHS number (Williams *et al.*, 2012; Herrett *et al.*, 2015; Stevenson, 2015). Within the NHS, GPs provide the initial consultation forum for health situations perceived as non-emergency i.e. not assumed to need hospital care (Wood and Martinez, 2004). Following an appointment at the general practice surgery, patients may be referred to specialists at the secondary care level (Garcia Rodriguez and Perez Gutthann, 1998). Secondary care data can be submitted back to the GP.

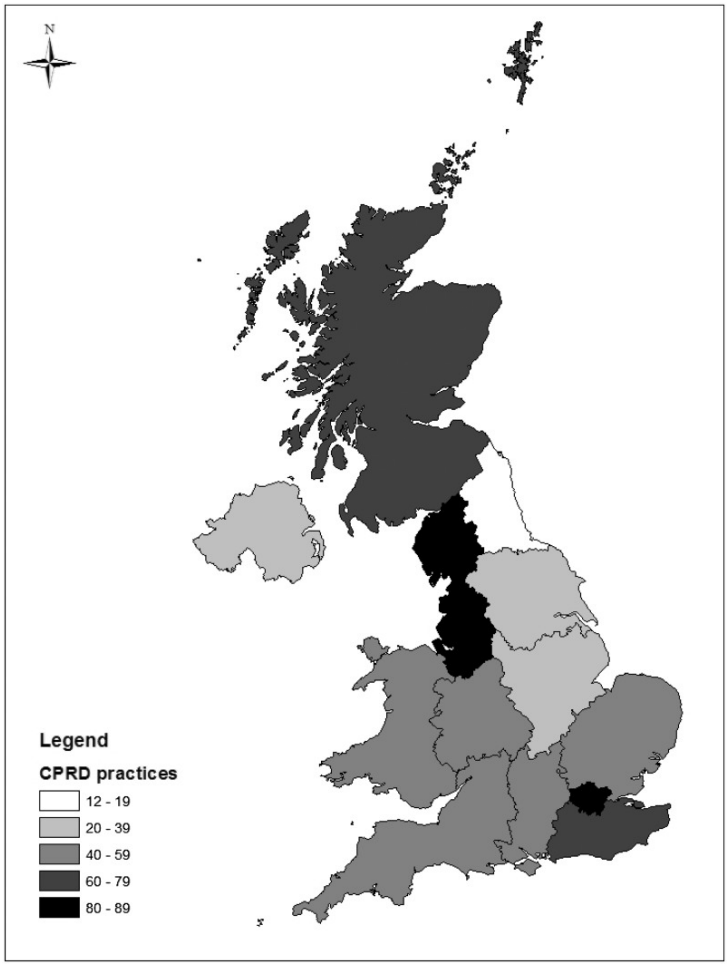
2.2.2. Quality and Outcomes Framework (QOF)

In England, the Quality and Outcomes Framework (QOF) was initiated in 2004 and is comprised of indicators (achievement measures) offering financial rewards to general practitioners. These indicators are centralised around three main domains: clinical, public health, and public health-additional services. Examples of indicators include documenting patients with cancer (clinical domain), documenting patients aged ≥45 years who have had a blood pressure reading within the preceding five years (public health domain), and the uptake of cervical screening for women aged 25 to 64 years (public health-additional services). QOF indicators are annually updated with the removal and addition of indicators (Primary Care Domain, NHS Digital, 2016). Melzer *et al.*, (2015) reported on the prevalence of 18 common diseases using the CPRD (n = 27,109) for the time frame 2003/2004 to 2011/2012 for the two age groups 65 to 84 years and ≥85 years. For the youngest age group, the prevalence of chronic kidney disease (CKD) stages 3-5 was 0.2% (95% CI 0.1, 0.6%) in 2003/2004 and 16.0% (CI 14.4, 17.9%) in 2011/2012, showing an absolute difference of 15.8% (CI 14.4, 17.2%). For the oldest age group these figures were 0.0% (CI 0.0, 0.3%) for 2003/2004 and 36.4% (CI 33.9, 39.1%) for 2011/2012 showing an absolute difference of 36.4% (CI 34.8, 38.0%). Between 2005 to 2007 there was a marked increase in the prevalence of CKD which may partly be explained by the introduction in 2006 of the QOF CKD register (Melzer *et al.*, 2015).

2.2.3. CPRD GOLD Dataset

De-identified primary care medical records are held by the research service within the CPRD GOLD dataset for UK patients registered with general practices which have opted to be part of this service (Herrett *et al.*, 2015; Stevenson, 2015). This constitutes approximately 8.8% of the UK population as of September 2014 (Stevenson, 2015). **Figure 2.1** shows the map of the CPRD practices which were considered up to standard on the 2nd July 2013. Patients may opt out of the service and to date less than 0.5% have declined to have their medical records used for research (Herrett *et al.*, 2015; Stevenson, 2015). The CPRD GOLD dataset reliably supplies information relating to health care, demographics, lifestyle factors, and referrals for further consultations in secondary care (Herrett *et al.*, 2015).

Figure 2.1| Distribution of the CPRD practices which were up to standard on the 2nd July 2013. Figure from (Herrett *et al.*, 2015)



2.2.4. Primary care records

Patients can receive health care consultations in person or via telephone conversations, which are logged electronically on a continuous basis (Herrett *et al.*, 2015). Medical records for patients from practices contributing to the CPRD GOLD dataset may span from their first consultation through to death, relocation, or until the last data collection for the practice. Medical health care data are collated monthly from the practices. During or following a medical consultation, symptoms, diagnoses, test results, health related behaviours, and prescriptions can be logged. Most diagnoses and symptoms are documented using Read Codes alongside the relevant date, with multiple codes permitted. Additional clinical data can be added numerically in association with the appropriate Read Code, e.g. weight can be recorded in kilograms. GP's can also supplement the records with text input, although this is not freely accessible for research purposes (Herrett *et al.*, 2015). **Table 2.1** presents details on the range of files available within the CPRD GOLD Dataset.

Table 2.1 | Data files available within the CPRD GOLD dataset

Data file	**Data content and example(s)**
Practice	Demographics e.g. region
Patients	Demographics e.g. age, gender, registration
Staff	Staff details e.g. nurse
Consultation	Type e.g. surgery consultation
Clinical	Medical diagnoses e.g. diabetes Symptoms e.g. exhaustion
Additional (linked to the clinical file)	Provides further details on diagnoses and symptoms e.g. weight in kilograms
Therapy	Prescriptions e.g. beta blockers
Referral	Referrals to specialists at secondary care level e.g. nose, throat and ear specialist
Test	Laboratory results e.g. estimated glomerular filtration rate
Immunisations	Vaccinations e.g. tetanus

2.2.5. CPRD data quality

There are internal reviews to improve the quality of the electronic health records conducted by CPRD personnel before release to researchers. Data are inspected at both the patient level (patient acceptability) and practice level (up to standard date). Checks at the patient level include registration status, ensuring consultations occur after the patient's year of birth, patients are aged <115 years, and gender is documented (Wood and Martinez, 2004; Williams *et al.*, 2012). At the practice level this involves checking the reported mortality is in line with the anticipated range and without gaps in data capture (Williams *et al.*, 2012; Herrett *et al.*, 2015). Following the introduction of the Quality and Outcomes Framework (QOF) in 2004, the recording of many diagnoses, health behaviours, and conditions has improved (Herrett *et al.*, 2015).

2.2.6. CPRD data linkage

Where possible the CPRD facilitates linkages to other datasets. Currently 75% of practices involved with the CPRD in England (overall 55% of the UK CPRD practices) can be linked to additional datasets, including Hospital Episode Statistics (HES), socioeconomic status, registered cancers, and deaths (Office for National Statistics [ONS]) (Williams *et al.*, 2012; Herrett *et al.*, 2015; Stevenson, 2015).

2.2.7. Validity and completeness of electronic health records

Although electronic records are advantageous in terms of the scale of data that can be analysed, it is important to consider the quality of the medical records. Herrett *et al.*, (2010) systematically reviewed the literature on the quality of medical records for diagnoses or syndromes and death records. The authors included 212 publications which comprised 357 validations of 183 unique diagnoses with most using external data sources. The median number of confirmed cases was 86.2% (range 33.0 to 100.0%) for validations carried out internally (n = 31) and 88.6% (range 24.0 to 100.0%) for those carried out externally (n = 143). More specifically, the median proportion of confirmed cases was 95.3% (range 74.0 to 100.0%) for the disease group neoplasms and 85.3% (range 48.0 to 100.0%) for circulatory diseases. Comparisons of the incidence and prevalence of diseases tended to be comparable to external data sources

except for rheumatoid arthritis and musculoskeletal diseases (Herrett *et al.*, 2010).

Similarly, Khan, Harrison and Rose (2010) conducted a systematic review of the validity of the GPRD electronic medical records, which included 49 papers with 40 of these validating diagnoses or lifestyle variables; the positive predictive value (PPV) tended to be over 50%. However, papers reporting on acute liver injury or acute renal failure reported lower PPVs (<50%). Three papers reported on the validity of myocardial infarctions (MI), with the lowest PPV reported as 81.6% (range 79.3 to 83.7%), and the highest PPV as 92.6% (range 88.3 to 95.7%). For diabetes, the PPV was reported as 98.6% (range 92.2 to 100.0%) (Khan, Harrison and Rose, 2010). Further details on the validity and completeness of the variables used in the CPRD analyses for **Chapters 4** to **6** are provided in **Table 2.2**.

Table 2.2 | Validity and completeness of variables from the CPRD used in this thesis

Variable	Validity and completeness
BMI	Bhaskaran *et al*., (2013) assessed the completeness of BMI records using a random sample of one million patients aged ≥16 years from the CPRD. From the period 1990-1994 to 2005-2011 there was an increase in the proportion of registered patients with a BMI record. For those aged 65 to 74 years 36.0% had a BMI record (within the preceding three years) in the time frame 1990-1994, whereas 67.0% had a BMI record for the time frame 2005-2011. Compared to the Health Survey for England data (HSE) 2010, the age and sex standardised mean BMI was considerably lower. The difference between the data sources was smaller when using more recent BMI values (within the previous 3 years) (Bhaskaran *et al.*, 2013).
Cancer	Boggon *et al*., (2012) reported on the concordance between cancer records within the CPRD and cancer registries. The concordance rate was reported to be 83.3% for the two sources using a sample of 101,020 patients during the time frame 1st April 1997-31st December 2006 (Boggon *et al.*, 2013). Dregan *et al*., (2012) also reported on the agreement between cancer records within the CPRD and cancer registries using a sample of 42,556 patients for the time frame 1st January 2002-31st December 2006. The concordance between the two sources was 91% (Dregan *et al.*, 2012).

Table 2.2 continued

Dementia	Dunn *et al*., (2005) reported on the survey results from GPs of 95 dementia cases (probable and possible) and 55 controls, who had been asked questions regarding diagnosis of dementia and the date of diagnosis. The first date of dementia diagnoses matched for 53.0%. The range for the date of diagnosis of the unmatched cases was between -7 and 0 weeks (Dunn *et al.*, 2005). Brown *et al*., (2016) compared dementia diagnoses in the CPRD, HES and a GP survey using a sample of 102,076 women enrolled in the Million Women Study. The concordance between a dementia record with HES and CPRD was 85.0% (CI 80.0, 88.0%). Read codes relating to the first mention of dementia tended to appear in the CPRD 1.6 years (SD 2.6 years) ahead of those in HES (Brown *et al.*, 2016).
Ethnicity	Mathur *et al*., (2014) reported on the completeness of ethnicity data within the CPRD and HES; with an additional comparison to the 2011 UK Census. For patients within CPRD practices during 1990-2012 (*n* = 12,099,672) 27.1% had an ethnicity record. For patients registered after April 2006 (18.2% of the whole sample) 78.3% had an ethnicity record. For HES inpatients (*n* = 51,965,028) 41.0% had a useable ethnicity record in 1997 and 86.0% in 2011. Combining CPRD and HES for patients registered after April 2006 resulted in 97.1% having useable ethnicity records. Concordance between the two data sources was 85% when using five broad ethnic groups. For 2011 the ethnicity breakdown was comparable between CPRD and the census (Mathur *et al.*, 2014).

Table 2.2 continued

Myocardial infarction	Hammad *et al*., (2008) reported on the PPV of Read/OXMIS codes to identify acute MI cases. GPs were asked to confirm the MI diagnoses with a response rate of 91.0%. The PPV was documented to be 93.0% (CI 90.0, 96.0%) from the 217 questionnaires The reported dates of MI tended to coincide within 15 days (90.0% of cases) (Hammad *et al.*, 2008). Furthermore, Herrett *et al.*, (2013) reported on the completeness and diagnostic validity of MI using CPRD, HES, MINAP and ONS. The authors identified patients with acute MI between January 2003 and March 2009. There was a record in CPRD for 74.5% of patients with a non-fatal MI. For HES and MINAP, this was 67.9% and 52.5%, respectively. An MI record was documented in CPRD, HES, and MINAP for 31.0% of patients with non-fatal MI. A MI record within two sources were reported for 63.9% of the patients. The incidence of MI recording ranged from 25.0% lower (CPRD) and 50.0% lower (MINAP) (Herrett *et al.*, 2013).
Smoking	Lewis and Brensinger (2004) compared smoking data from the GPRD, a survey of GPs, and the 1996 Living in Britain National Household Survey. Using the survey responses from the GPs (136 surveys), the sensitivity of current smoking was 78.0% (CI 52.0, 94.0%) and the PPV was 70.0% (CI 46.0, 88.0%). For former smoking the results were 53.0% (CI 28.0, 77.0%) and 60.0% (CI 32.0, 84.0%) respectively. Compared to the survey current smoking in the GPRD was 79.0% and former smoking 29.0% of these rates (Lewis and Brensinger, 2004). Moreover, Booth, Prevost and Gulliford (2013) compared smoking records within the CPRD (n = 279,682) to the HSE for the period 2007-2011. The difference between the prevalence of current smoking tended to be <1.0% between the sources. The prevalence of non-smoking was similar between the two data sources. The prevalence for former smoking was lower within the CPRD with estimates for males of 26.7% and women 22.9% compared to 31.3% and 25.0% from the HSE (Booth, Prevost and Gulliford, 2013b).

2.2.8. Strengths of the CPRD

Major strengths of the UK CPRD database include that it is longitudinal and incorporates a large number of patients and variables (Herrett *et al.*, 2015; Stevenson, 2015). The large scale improves statistical power to detect associations between exposures and health-related outcomes and the opportunity to research rare conditions (Garcia Rodriguez and Perez Gutthann, 1998; Wood and Martinez, 2004). Primary care consultations can be incorporated with links to socioeconomic data, hospital admissions, cancer registrations, and patient deaths. Sole use of one dataset (e.g. primary care) may not capture medical events occurring at different levels (e.g. secondary care) and thus estimates on chosen health outcomes may be biased (Herrett *et al.*, 2013). CPRD patients are reported to typify the general population regarding age, gender, and ethnicity (Herrett *et al.*, 2015). Similarly, patients in practices which have been externally linked to other datasets (HES, disease registries, and ONS) have been reported to be representative of all the patients within the CPRD (Gallagher, Puri and Van Staa, 2011). CPRD data undergoes a quality review before release to researchers (Herrett *et al.*, 2010, 2015). QOF rules have also had an impact on the standard of the electronic health records.

2.2.9. Suitability of the CPRD

This dataset was chosen for my statistical analyses presented in **Chapters 4** to **6** due to the large size and the linkage to additional datasets including HES, the index of multiple deprivation (IMD), and ONS for registered deaths. Analyses can be stratified based on patient characteristics whilst maintaining a large sample size. Outcome ascertainment of coronary heart disease (CHD) is improved substantially with links to HES. In **Chapter 4** I present an analysis where I have estimated the BMI associations, using the WHO BMI Classification, with mortality across progressively older age groups, and for subgroups of 'healthier agers' and 'non-healthier agers' due to a paucity of studies that have provided recent BMI estimates. In **Chapter 5** I extend on the work presented in **Chapter 4,** using a re-defined BMI referent group from the estimated continuous BMI association with mortality. This revised referent group was used to estimate the associations for mortality, incident CHD, and Type 2 diabetes. The rationale for this analysis was that persons within the lower end of the conventional BMI Normal range may be

at a heightened risk for mortality and thereby mortality risk estimates for higher BMI values may be distorted. Additionally, there has been a lack of studies which have presented risk estimates for CHD and type 2 diabetes across narrower age groups. In **Chapter 6** I present an analysis where I estimated the BMI associations with incident dementia using a revised referent BMI group estimating short (0 to <10 years) and long (≥10 to 14.9 years) term risks, due to inconsistent results in the literature regarding the association for the BMI Obese range.

2.2.10. Potential issues with using the CPRD

One of the key issues with the CPRD is that data are not collected for research purposes (Herrett *et al.*, 2015). Whether a medical event is recorded is determined by the general practitioner. Medical data may be collected during health checks (e.g. NHS health check) or opportunistically. The number of variables which are complete and useable varies for CPRD patients, for example lifestyle factors could be documented more often for subsets of patients with certain health conditions (Welch and Bartlett, 2014; Herrett *et al.*, 2015). Using complete cases only may produce biased estimates and can severely reduce the sample size. Variables may not be documented for the same baseline date and, therefore, the appropriate time frame for incorporating earlier healthcare records (or prospective healthcare records) will need to be considered (Sterne *et al.*, 2009; Herrett *et al.*, 2015). Transference of data collected from secondary care may be lacking relevant detail due to being completed at the general practice level.

Chronic diseases may only be documented once and this should be taken into consideration when deciding appropriate time frames for selecting subsets of patients or confounders (Lawson, Sherman and Hollowell, 1998). It could be assumed that patients without pre-specified Read Codes for health outcomes may be free of that disease or condition of interest (Herrett *et al.*, 2015). This could be due to differences in Read Codes selected by health practitioners, the documentation of symptoms and diagnoses in free text, and from patients avoiding primary care consultations.

Moreover, the Read Codes chosen during analyses to identify a specific disease may differ leading to discrepancies between studies, for instance in prevalence estimates (Khan, Harrison and Rose, 2010). Additionally, clinical presentations of diseases may be hard to distinguish due to the Read Codes chosen. For instance, Bhattarai *et al*., (2012) evaluated the Read Codes used to identify incident CHD using a random sample of 300,020 patients aged >30 years for the time frame 1st January 2004 - 30th June 2010, and documented that 39.6% were reported with a diagnostic code of 'Other CHD' (Bhattarai *et al.*, 2012). Furthermore, Tate *et al*., (2017) reported that estimates on the incidence of type 2 diabetes may be dependent on the chosen Read Codes. The incidence of type 2 diabetes was reported to have increased up to 2004, stagnated to 2009, and decreased thereafter when only diagnosis codes were used for 684 practices within the CPRD. In contrast, when non-diagnosis codes (e.g. codes suggestive of diabetes) were additionally used the incidence of type 2 diabetes increased up to 2012 (Tate *et al.*, 2017).

2.2.11. CPRD approval

Before researchers can use the CPRD GOLD and linkage datasets, all research protocols need to be approved by the MHRA Independent Scientific Advisory Committee (ISAC). During my PhD, I was involved in collaborating on the research proposal to enable access to use the CPRD for my statistical analysis. The overall aim of the protocol was to "improve evidence on predictive value of general practice recorded risk factors for cardiovascular disease onset and mortality, at various stages of later life". My contribution to the approval included identifying the risk factors (including BMI), confounders, and the outcomes (mortality and cardiovascular endpoints) to be analysed. Furthermore, I reviewed the literature for the predictive value of risk factors (high cholesterol, high blood pressure, smoking, diabetes, and high BMI) with mortality and cardiovascular mortality in later life and contributed to writing the background section. I finalised the Read Codes to be used for the various risk factors based on a literature review and discussions with clinicians within the research group. The CPRD has been granted Multiple Research Ethics Committee approval (05/MRE04/87) to undertake purely observational studies, with external data linkages including HES and ONS mortality data. The work of CPRD is also covered by NIGB-ECC

approval ECC 5-05 (a) 2012. My CPRD analyses were approved by the Independent Scientific Advisory Committee for MHRA database research (ISAC) under protocol number 14_135 (2014).

2.2.12. Variables used for data analysis with the CPRD

The analyses presented in **Chapters 4** to **6** use a sample of registered patients who have been linked to HES, the IMD 2007 dataset, and ONS. These data linkages are only available for patients residing in England. Outcome ascertainment for the chosen health outcomes is substantially improved with the linkage to the HES. All analyses used BMI as the exposure variable, hence patients were required to have a BMI record. The earliest baseline date was the 1st January 2000 and patients were required to be aged ≥60 years at the time of the BMI record.

Read Codes for defining variables and health outcomes were derived from the QOF Business Rules (version 18.0), from published literature of Read Codes, and from two clinicians who were blinded to each other's work. Any discrepancies were resolved by a third clinician. A similar approach was undertaken for defining health outcomes and variables from the HES regarding ICD 10 codes. For health behaviour measures such as BMI, the additional field containing numerical data was checked against the Read Codes documented at the same entry time. Read Codes which were deemed not to relate to the measurement were thus excluded (and the relating measure) during the data preparation stage. **Table 2.3** provides information on the variables used in the CPRD analyses presented in **Chapters 4** to **6.** Details on the numbers of participants and missing/unrecorded variables will be presented in each chapter.

Table 2.3 | Variables used from the CPRD GOLD dataset and external linkages

Variable	**Data available from CPRD Gold dataset plus external linkages and additional analyses details**
Patient characteristics	
Age	• Month and year of birth are provided within the demographics file. • For the analyses the day of birth is set to the middle of the month.
Gender	• Gender: male, female, or indeterminate are provided within the demographics file. • Only a small number are classified as indeterminate.
Ethnicity	• CPRD GOLD database and HES contains data on ethnicity improving completeness of data.
Anthropometric measures	
Weight	• Weight is entered numerically in the additional clinical file which aligns with the clinical file.
BMI	• BMI is entered automatically following entry of a weight measure and is reported in the additional file. • For the analyses the numerical data were used rather than medical codes associated with obesity e.g. “on examination, obese”. Medical codes would not provide an indication of the patient’s BMI value. • Booth, Prevost and Gulliford, (2012) reported that medical diagnostic codes for obesity were not consistently reported. In a sample of 67,000 patients with Obesity, defined by diagnostic codes or BMI ≥30.0 kg/m^2, aged 18 to 100 years during the time frame 1997-2007, only 29.7% had a diagnostic code recorded. BMI values were available for 99.2% of the patients (Booth, Prevost and Gulliford, 2013a).

Table 2.3 continued

Lifestyle and socioeconomic circumstances	
Smoking	• Smoking status was based on GP recorded Read Codes within the clinical file. • Patients were classified as current smokers, ex-smokers, never smokers, and not recorded.
Alcohol	• Alcohol status was based on GP recorded Read Codes and units of alcohol per week (where available) from the clinical and additional file. • Patients were classified as heavy drinkers, non-drinkers, current drinkers, former drinkers, and not recorded. • Heavy drinkers were defined as >35 units for females and >50 units for males.
Physical activity	• Physical activity was recorded in CPRD as inactive, gentle activity, moderate activity, vigorous activity, or not recorded within the clinical file.
Relative social deprivation	• Relative social deprivation was recorded using the IMD 2007 dataset.
Prevalent/ incident disease plus mortality	
-Asthma -Atrial Fibrillation -Cancer -Chronic Kidney Disease stages 3-5 -Chronic Obstructive Pulmonary Disease -Coronary Heart Disease -Dementia -Depression -Epilepsy -Heart Failure -Hypertension -Hypothyroidism -Mental Health -Stroke -Type 2 Diabetes	• Based on CPRD Read Codes and ICD codes for HES. • The cause, location, and date of deaths are provided by both ONS and those recorded within the CPRD GOLD. ICD codes are used for the cause specific deaths.

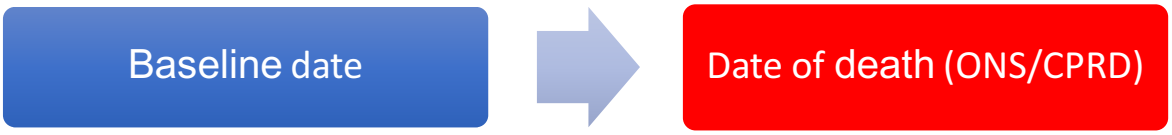
2.2.13. Follow-up periods

Patients within practices which have opted to be part of the CPRD research service can be followed up from the chosen baseline period to the health outcome of interest (e.g. CHD), transfer out date (e.g. patient has transferred from the practice due to relocation), last collection date of the practice, or date of death. For patients who transferred out of practices but have been registered to have died, the date of death can be used as this is recorded within the ONS dataset. **Figure 2.2** depicts the follow-up periods for mortality for patients who died and patients who did not die. For patients who transferred out of practices, the transfer out date is used when morbidity outcomes (e.g. MI) are the focus, as the patient may have had the chosen health outcome after the transfer out date. **Figure 2.3** depicts follow up-periods for morbidity (e.g. MI).

Figure 2.2 | Follow-up periods for mortality

Patients who died

A) Patient remains in the CPRD practice



B) Patient transfers out of the CPRD practice. Date of death can be obtained from ONS.

Patients who survived

C) Patient remains in the CPRD practice

D) Patient transfers out of the CPRD practice.

Figure 2.3 | Follow-up periods for morbidity (e.g. myocardial infarction)

Patient has a MI

A) Patient remains in the CPRD practice and has a MI.

Patient dies during the follow-up

B) Patient dies during the follow-up period

Patient does not have a MI during the follow-up period

C) Patient remains in the CPRD practice

Patient transfers out of the practice (no MI recorded prior to this date)

D) Patient transfers out of the CPRD practice.

2.2.14. Challenges of using electronic health records

Electronic health medical records have the advantage that research questions that may not have been feasible on a large scale can be addressed. However, there are many challenges with using this data source. The quality and completeness of medical records may alter with new or updates to health guidelines and financial incentives (such as QOF) throughout time, and similarly the Read Codes chosen for symptoms and diagnoses (McDonald *et al.*, 2016). It is important to consider which patients, and essentially, why patients access primary and secondary care. Patients may access over the counter medicines which would not be captured. A patient's symptoms may trigger the collection of lifestyle variables and testing of conditions (e.g. ordering a blood test), in contrast to volunteer studies, and therefore affect the generalisability. Volunteer studies tend to collect baseline measures on all participants who are typically healthier (Bhaskaran *et al.*, 2013; McDonald *et al.*, 2016). New patients registering with practices have been shown to increase the reported incidence of acute and chronic conditions, due in part to joining practices when symptoms arise (Lewis *et al.*, 2005).

2.2.15. Reporting checklists

In 2015, RECORD was published, a reporting checklist for analyses which use routinely collected health data, this being an extension of the STROBE guidelines (von Elm *et al.*, 2007; Benchimol *et al.*, 2016). These extensions include: providing additional details about the data source (time frame and region) plus other linkages, selection criteria for the population, codes used, and implications of using health records. This checklist was used for the reporting of the published paper (Bowman *et al.*, 2017) which has been adapted in **Chapters 4** and **5**.

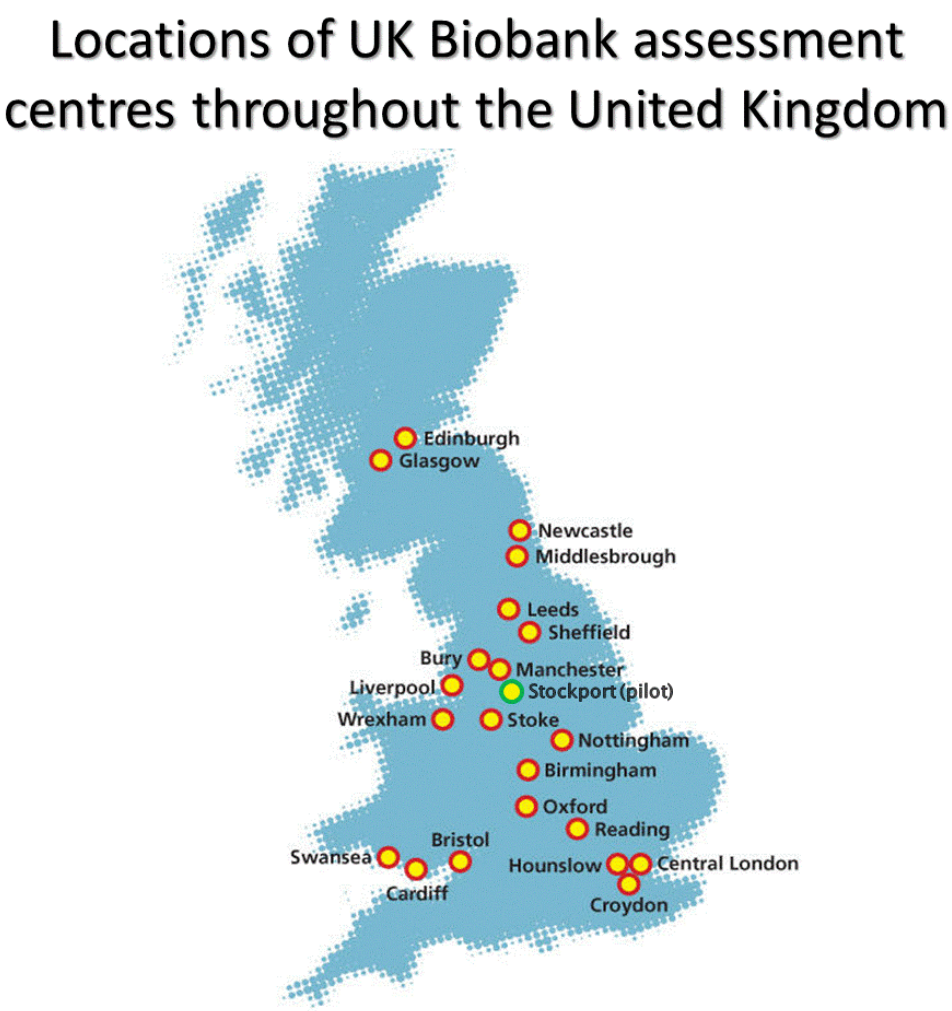
2.3. Overview of the UK Biobank

The UK Biobank is a large prospective volunteer study (Allen *et al.*, 2012). The UK Biobank was constituted by the Medical Research Council, the Wellcome Trust, the Department of Health, and the Scottish Government (Trehearne, 2016). The overarching aim was to enable investigation of environmental, lifestyle, and genetic exposures to a broad range of health outcomes which can occur in middle age and in later life (Allen *et al.*, 2012; Sudlow *et al.*, 2015; Trehearne, 2016). Major strengths of this dataset are the wealth of variables concurrently collected at baseline with external links to HES and cancer registries.

2.3.1. UK Biobank participants

Adults aged 40 to 69 years who were within a 25-mile radius of one of the 22 assessment centres (across England, Scotland and Wales) and registered with the NHS were eligible to participate (Allen *et al.*, 2012; Manolio *et al.*, 2012). **Figure 2.4** shows the UK Biobank assessment centres. Recruitment took place during 2006 to 2010 with postal invitations (Sudlow *et al.*, 2015; Trehearne, 2016). Most of the volunteers were aged 40 to 69 years (range 37 to 73 years) (UK Biobank, 2017a). The recruitment process ensured that participants were from diverse socioeconomic backgrounds and ethnic origins with the inclusion of participants from rural villages to urban areas (Manolio *et al.*, 2012; Sudlow *et al.*, 2015; Trehearne, 2016). Volunteers are able to withdraw from the study at any time, although there have been few cases in which this has occurred (Trehearne, 2016).

Figure 2.4 | UK Biobank assessment centres (UK Biobank, 2017b)



The overall response rate was 5.5% (Allen *et al.*, 2012), with 502,632 volunteers recruited (UK Biobank, 2017a). A recent analysis compared the UK Biobank volunteers to the UK Census, HSE, and ONS. The ethnicity data for the UK Biobank volunteers was less comparable to the 2011 UK Census (95.0% white ethnicity for the UK Biobank compared to 91.0% for the Census). For those aged 65 to 69 years both the incidence of cancer and mortality rates were reported to be lower than the general population (cancer: 31.0% lower for the males and 42.0% lower for females, mortality: 56.0% lower for males and 68.0% lower for females). The prevalence of current smokers and the prevalence of obesity is lower for the UK Biobank participants compared to the HSE, therefore, inferring healthy volunteers (Fry *et al.*, 2016).

Volunteers provided their consent at the assessment centre alongside extensive information on medical history, lifestyle and environmental exposures through touch

screen questionnaires (reducing transcription errors) and personal interviews (Allen *et al.*, 2012; Manolio *et al.*, 2012; Sudlow *et al.*, 2015; Trehearne, 2016). Anthropometric measurements and biological samples were also collated during the assessment centre visit (Allen *et al.*, 2012). The volunteers have been linked to cancer registries, hospital admissions, and mortality databases. Volunteers are, therefore, continuously followed up for health outcomes using these external dataset linkages. All of the data provided to researchers are de-identified (Sudlow *et al.*, 2015).

2.3.2. Strengths of the UK Biobank

A major strength of the UK Biobank is that detailed information was collated on a broad range of exposures at the assessment centre visit (Collins, 2012). The baseline visits were conducted during 2006-2010, enabling researchers to provide updated quantification on associations (Allen *et al.*, 2012). Lifestyle factors and physical measures were collected at the same time point. The large sample size improves the range of exposures, health outcomes, and thus the statistical power to detect associations (Trehearne, 2016). For each exposure of interest several health conditions can be addressed (Allen *et al.*, 2012). Recall bias and reverse causation are minimised from the prospective study design; data on exposures can be ascertained before the diagnosis of the health outcome(s) of interest (Collins, 2012). The external linkage to cancer registries, hospital admissions, and mortality is another advantage to the UK Biobank improving the accuracy of both prevalent and incident diseases (Collins, 2012). There is a continual update of hospital admissions, cancer registrations, and deaths. The recruitment process ensured there was diversity in terms of socioeconomic background, ethnic origin, area of residence, and exposures improving the generalisability (Manolio *et al.*, 2012; Sudlow *et al.*, 2015; Trehearne, 2016).

2.3.3. Suitability of the UK Biobank

This dataset was chosen for the statistical analyses presented in **Chapters 7** and **8**. One of the key strengths of this dataset is that lifestyle variables were collected at the same time point rather than opportunistically or during health checks as is the case for the CPRD. A further strength is that a range of anthropometric measures were collected at baseline (CPRD has limited data on anthropometric measures other than

weight and height). This allows comparisons of different body measures and the combining of physical measures. In **Chapter 7** I present an analysis where I compared established measures of body fat distribution and body composition to BMI for mortality prediction for 'healthier agers' within the seventh decade of life and described the concordance between categories of BMI and these different measures. In **Chapter 8** I present an analysis where I estimated the associations between combined measures of BMI and waist-to-hip ratio (WHR) with mortality, and incident CHD.

2.3.4. Potential issues with using the UK Biobank

In a similar manner to the CPRD, there is also the issue that some participants may be missing data. Volunteers could opt to select the "prefer not to answer" or "do not know" for the touchscreen questionnaire (UK Biobank, 2013). To date, there is no data available on primary care consultations (this is planned to be linked in the future). This could lead to an underestimation of diagnoses which may be more commonly recorded at the primary care level such as diabetes.

2.3.5. Variables used for data analysis with the UK Biobank

The analyses presented in **Chapters 7** to **8** use a sample of 'healthier agers' from the UK Biobank. For these chapters I included participants aged 60 to 69 years. '**H**ealthier agers' were non-smokers without cancer, dementia, or heart failure. **Table 2.4** provides information on the variables used in the analyses presented in **Chapters 7** and **8.** The ICD-10 codes and combining of data from the touchscreen questionnaire was shared and agreed by clinicians, research fellows, and myself all from the Epidemiology and Public Health Group. The ICD-10 codes for each of the diseases were derived from relevant ICD codes in the literature and by two clinicians who were blinded to each other's judgements. Any disagreement in coding was resolved by a third clinician.

The touchscreen questions asked to participants were based on previous surveys including the HSE, longitudinal studies and expert opinions (UK Biobank, 2007). The physical activity questions asked to the volunteers were based on a validated survey (Craig *et al.*, 2003).

Adiposity measures and other components of body composition

UK Biobank staff were trained and monitored, adhering to a standard protocol for physical measures (UK Biobank, 2007, 2014). Weight, fat mass, fat free mass, and body fat percentage were measured using the Tanita BC-418 MA body composition analyser for participants who had bio-impedance (BIA) measures taken. Body composition measures are quickly determined using in built algorithms. Advantages of using this analysis include accurate weight measurement (+/- 0.1 kg), recalibration is required infrequently and automatic transferal of readings to IT systems, removing transcription errors. These advantages combined with the relatively low cost of measurement can make this technique preferable to imaging techniques such as DXA, CT, and MRI. The European consensus on defining and diagnosing sarcopenia concluded that BIA could be a portable substitute to DXA (Cruz-Jentoft *et al.*, 2010). Studies have shown that compared to DXA the estimated fat mass may be lower for both genders (Völgyi *et al.*, 2008), lower for females and higher for males (Mally *et al.*, 2011), and comparable for both genders (Pietrobelli *et al.*, 2004). Discrepancies may be due to using different populations compared to the populations on which the algorithms were derived. Measures which are manually entered (e.g. height, waist circumferences and hip circumferences) which are deemed to be implausible are flagged instantaneously.

Table 2.4 | Variables used from the UK Biobank and external linkages

Variable	Data available from the UK Biobank and additional analyses details
Volunteer characteristics	
Age	• Month and year of birth were collected prior to the initial visit from local NHS Care Trust registries (UK Biobank, 2016). • For the analyses the day of birth is set to the middle of the month.
Gender	• Collated from local NHS Care Trust registries: female or male (UK Biobank, 2017a).
Ethnicity	• Participants first completed a question on their ethnic group with responses including: White, Mixed, Asian or Asian British, Black or Black British, and Chinese. • Some participants were asked further about their ethnic background dependent on response to the ethnic group question (UK Biobank, 2013).
Anthropometric measures	
Weight	• Collected by nurses and health technicians during the assessment centre visit with a Tanita BC418MA body composition analyser or with standard scales (for participants who did not undergo BIA measures) (UK Biobank, 2007, 2014).
Height	• Collected by nurses and health technicians during the assessment centre visit using Seca 240cm height measure (UK Biobank, 2007, 2014).
BMI	• Derived from height and weight measures taken at baseline.
Waist	• Collected by nurses and health technicians during the assessment taken with a Seca 200cm tape measure at the natural indent (UK Biobank, 2007, 2014).
Hip	• Collected by nurses and health technicians during the assessment taken at the widest part with a Seca 200cm tape measure (UK Biobank, 2007, 2014).

Table 2.4 continued

Anthropometric measures continued	
-Whole body fat mass/ -Whole body fat free mass -Body fat percentage	• Collected by nurses and health technicians during the assessment using the Tanita BC418MA body composition analyser (UK Biobank, 2007, 2014).
Weight loss	• Participants were asked to compare their weight at baseline to the previous year with responses including: no change, gained, and lost (UK Biobank, 2013).
Lifestyle factors and socioeconomic circumstance	
Smoking	• Derived from multiple questions from the touch screen questionnaire which participants completed during the assessment centre visit. Participants were asked whether they currently smoked tobacco. • Participants who responded that they did not currently smoke were subsequently asked how often they smoked tobacco in the past (UK Biobank, 2013).
Alcohol intake	• The frequency of alcohol intake was recorded by the volunteers on the touch screen questionnaire during the initial assessment visit. Responses included: never, special occasions, once to three times per month, once or twice per week, three or four times per week, daily or almost daily (UK Biobank, 2013).
Physical activity	• The volunteers also completed questions on their duration and intensity of physical activity in a typical week (UK Biobank, 2013).
Educational Attainment	• During the assessment participants were asked about their educational qualifications. Participants could select multiple choices (UK Biobank, 2013). Responses included: NVQ/HND/HNC/ equivalent, CSEs/equivalent, O levels/ GCSEs/ equivalent, A levels/AS levels/equivalent, other professional qualifications (nursing/ teaching), College/University degree. The questions were adapted from those used within the HSE (UK Biobank, 2007, 2013).

Table 2.4 continued

Prevalent/incident disease and mortality	
-Cancer -CHD -Dementia -Heart Failure -Type 2 Diabetes	• Data on prevalent and incident diseases were derived from the touchscreen questionnaire, personal interviews, ICD-10 codes for hospital admissions (HES), and ICD-10 codes from the cancer registries. • Cancer registrations were provided by the Health & Social Care Information Centre (HSCIC) for England and Wales and by the Information Services Department for Scotland. Cancer registrations are available from the 1980s for England and Wales and 1950s for Scotland. • Hospital admission data was provided by HES (HSCIC) for England, Patient Episode Data for Wales (Secure Anonymised Information Linkage) for Wales, and Scottish Morbidity Records for Scotland. Hospital admission data are currently available from 1997 for England, 1999 for Wales, and 1981 for Scotland (Biobank, 2009). • Data on deaths (cause and date) for England and Wales was provided by the HSCIC and by the ISD for Scotland (Biobank, 2009).

2.4. Statistical analysis

2.4.1. Statistical packages

For the analyses reported in **Chapters 3** to **8** I used Stata versions 13 and 14 and R versions 3.1.2 and 3.2.0. These statistical packages are particularly suitable due to their ability to manage large datasets. Detailed below are the main statistical methods I used throughout this thesis. An overview of each methodology is provided within each of the subsequent chapters (**3 to 8**).

2.4.2. Meta-analysis

In **Chapter 3** I conducted a review and meta-analysis of cohort studies which reported mortality risk estimates for adults aged ≥65 years for the BMI Overweight range and/or BMI Obese-1 range. This involved searching Embase, Medline, and Scopus electronic databases up to 13th August 2016 which were limited to English language articles published from 1st January 2000. The inclusion criteria were: cohort studies with ≥3y of follow-up, participants aged ≥65 years, minimum of 1,000 participants within each sub-group, risk estimates reported for the BMI Overweight range and/or BMI Obese-1 range, and all-cause mortality as the outcome. A meta-analysis involves combining several studies to provide a pooled estimate with the assumption that this will be more precise and reliable (due to the increased statistical power) than those reported from the individual studies (Peacock, 2011; Bowers, 2014). For the analysis presented in **Chapter 3** this involved pooling the hazard ratios for mortality for the BMI Overweight and BMI Obese-1 range. In **Chapter 3** I used fixed effects models to combine reported mortality risk estimates for individual studies (within studies) e.g. where estimates were reported for males and females separately these were pooled used fixed effects, as it was assumed that each study was estimating one single fundamental effect (Peacock, 2011). I used the random effects approach when analysing multiple studies as it was assumed that there would be variability amongst the participants within each study and variability between the analyses. This model, however, tends to produce wider confidence intervals than those from fixed effects due to greater variability attributed to the individual studies (Peacock, 2011). I used the I^2 statistic to test the heterogeneity between the included analyses (Peacock, 2011; Bowers, 2014). Values

above 50% are considered large, 25 to 50% modest, and <25% low (Patsopoulos, Evangelou and Ioannidis, 2008). Advantages of using a meta-analysis approach include summary estimates can be derived as the statistical power is increased, publication bias can be assessed, and heterogeneity between the individual studies can be assessed. Limitations of meta-analyses include the quality of the studies included may vary, the choice of model adjustments may differ between studies, publication bias, and the heterogeneity of studies.

2.4.3. Directed Acyclic Graphs

In **Chapter 4** I use a Directed Acyclic Graph (DAG) to model the preconceived variables which may affect the chosen exposure and outcome of interest. In this case, BMI was the exposure and mortality was the outcome. This DAG was constructed using the webpage DAGitty (http://dagitty.net). The graphic contains no cycles, with each arrow pointing in one direction to imply that a variable could cause/influence the other variable (Vanderweele and Robins, 2007). This allows the identifications of confounders and mediators (Vanderweele and Robins, 2007; Shrier and Platt, 2008). Conditioning on disease states has been shown to accentuate bias by confounders such as smoking (Preston and Stokes, 2014; Banack and Kaufman, 2015).

2.4.4. Logistic regression

Logistic regression models are based on the logit concept and are suitable when the outcome is binary (Peng, Lee and Ingersoll, 2002). The logarithm of the odds of the outcome is modelled as a linear function of explanatory variables. The odds of the outcome for both the exposed and unexposed group can then be derived, before or after adjustment for confounding variables. Observations are assumed to be independent and the binary outcomes are assumed to follow a binomial distribution. These models can be used to test cross sectional associations e.g. between BMI and prevalent diabetes, and prospective associations e.g. BMI and incident diabetes. In **Chapter 4** logistic regression models were used to test the associations of 15 major diseases with measured weight loss. A common rule of thumb is that the sample size for these models should be such that there are at least 20 or more outcomes in each of the binary groups per variable included in the model, and this was checked within each of my datasets (van der Ploeg, Austin and Steyerberg, 2014) . This condition was

easily satisfied for both the CPRD and the UK Biobank analyses due to the large number of outcomes. A limitation of logistic regression models includes the requirement of large sample sizes, although for these analyses this was not relevant.

2.4.5. Survival analysis

The UK Biobank includes baseline data on exposures and follow up data for mortality and incident health outcomes from hospital admissions with dates provided for all. Similarly, in the CPRD dates are derived for when the exposure of interest was measured and dates are provided for mortality and incident health outcomes from GP surgery visits and hospital admissions. This lends both datasets to survival analysis due to the time element between the exposure and health outcome of interest (Bowers, 2014). These methods compute survival probabilities (Peacock, 2011). Participants who withdraw early and those who are alive at the end of the study period are censored (Peacock, 2011; Bowers, 2014). In the UK Biobank participants are censored only at the end of the follow up as all data are removed for any participant who wishes to withdraw from the study. In the CPRD participants may be censored if they change to a new GP surgery. Survival models can incorporate censored observations (Peacock, 2011).

2.4.6. Cox proportional hazard models

Cox proportional hazards models are often used to assess associations between a binary exposure and the time to an outcome event. Researchers can include and adjust for several confounders in these models. The hazard rate is defined as the instantaneous risk of the event conditional on having survived to that point in time. The hazard ratio is then the ratio of hazard rates in two groups. A key assumption of these models is that the hazard ratio between exposure groups is constant over the time period, referred to as the proportional hazards assumption (Peacock, 2011; Bowers, 2014). This assumption can be tested using Schoenfeld residuals and I checked this assumption for all my analyses. Cox proportional hazards models were used to estimate the association between BMI (and other anthropometric measures) with mortality using the CPRD and UK Biobank datasets (**Chapters 4** to **8**).

2.4.7. Spline models

Spline models can be used to explore the shape of the relationship between continuous functions such as BMI and mortality with the results being graphically displayed using a smooth non-linear curve. The model fits a series of non-linear functions (e.g. cubic polynomials) which are constrained to join at a series of pre-specified points referred to as knots. Spline models were used in **Chapter 5** and **Chapter 7**.

2.4.8. Competing risks models

With ageing, there is an increased likelihood that other health outcomes may occur before the health outcome of interest. For example, a competing risk in a study where the primary outcome of interest is the incidence of second hip fracture would be deaths following the first hip fracture (Berry *et al.*, 2010). These competing risks (e.g. death following the first hip fracture) can impede the chosen health outcome and models should address this issue (Wolbers *et al.*, 2009). As highlighted in **Chapter 1** and in **Chapter 5** several analyses reporting on the association between BMI and either CHD, diabetes, or dementia did not incorporate the competing risk of death into the models. Within my data analyses I used the Fine and Gray Competing Risk Models as it is extensively utilised (Wolbers *et al.*, 2009). This model considers the existence of competing risks and reports the cumulative incidence of the health outcome of interest, which is reported as the sub-distribution hazard ratio (sHR) (Wolbers *et al.*, 2009; Berry *et al.*, 2010). I used this model in **Chapters 5, 6** and **8.**

2.4.9. Multiple imputation

As stated in the potential issues for using the UK CPRD and the UK Biobank, an important challenge in using these datasets is that relevant variables (baseline covariates as well as outcomes) may be missing. One approach to manage this is to use multiple imputation, assuming that we view subjects without the record of interest as a missing-data problem (Welch and Bartlett, 2014). Multiple imputation is based on the Bayesian concept and is widely used to manage missing variables (Sterne *et al.*, 2009; Peacock, 2011; Welch and Bartlett, 2014). This method imputes data for missing fields utilising values from related covariates (Peacock, 2011). Multiple datasets are, therefore, imputed due to the uncertainty surrounding the missing values (Sterne *et*

al., 2009; Peacock, 2011; Welch and Bartlett, 2014). The appropriate statistical techniques for analysing the complete data can then be carried out on each of these data sets (Sterne *et al.*, 2009; Peacock, 2011). The assumption is made when using multiple imputation that values are missing at random: this means that given the observed data, the data are missing independently of the unobserved data. Where this assumption cannot be made, the data are said to be missing not at random and more complex methods are needed that account for the missing data mechanism. Multiple imputation was used in **Chapter 5** to impute smoking and alcohol records. This was not used for the UK Biobank analyses as missing patient variables were not considered to be missing at random. There were a limited number of participants missing variables on smoking, alcohol intake, or educational attainment.

2.4.10. Model selection

Model selection involves assessing several candidate models (Wagenmakers and Farrell, 2004). One method which is widely used is the Akaike information criterion (AIC) (Jones, 2011; Fabozzi *et al.*, 2014). The lowest value for this criterion is considered the "best" model approximating the data when comparisons are made using the same data source (Jones, 2011; Fabozzi *et al.*, 2014). I used this method to compare established measures of body fat distribution and body composition to BMI for mortality prediction for 'healthier agers' within the seventh decade of life, which is presented in **Chapter 8**.

Chapter 3: A review and meta-analysis on the BMI Overweight and BMI Obese-1 range with all-cause mortality

Table of Contents

List of Tables for Chapter 3

List of Figures for Chapter 3

3.1. Summary

Background: Equivocal risks for mortality have been reported for older adults (≥65 years) within the body mass index (BMI) defined Overweight (25.0-29.9 kg/m^2) and BMI Obese-1 (30.0-34.9 kg/m^2) ranges relative to those within the conventional BMI Normal range (18.5-24.9 kg/m^2). Inclusion of smokers, adults with conditions associated with weight loss, and the choice of BMI referent group may distort mortality risk estimates.

Objective: To conduct a review and meta-analysis of cohort studies which reported mortality risk estimates for adults aged ≥65 years for the BMI Overweight range and/or BMI Obese-1 range. To determine the influence of specific exclusions (smokers, conditions associated with weight loss, and early follow-up) and combinations of exclusions with consideration of the BMI referent group for the risk of mortality.

Methods: Embase, Medline and Scopus electronic databases were searched up to 13th August 2016 and were limited to English language articles published from 1st January 2000. The inclusion criteria were: cohort studies with ≥3 years of follow-up, participants aged ≥65 years, minimum of 1,000 participants within each sub-group, risk estimates reported for the BMI defined Overweight range and/or BMI Obese-1 range, and all-cause mortality as the outcome. The baseline period, study characteristics (age, gender, sample size), exclusion criteria, the method of obtaining height and weight, the follow-up period, the number of deaths, model adjustments, the BMI groups, and the reported mortality risk estimates were extracted from each study. Random effects models were used to pool effect sizes.

Results: Forty studies were included in this review, with all studies reporting mortality risk estimates for the BMI Overweight range and 19 studies for the BMI Obese-1 range. Summary mortality risks were calculated relative to those with BMI values within the Normal range. Summary hazard ratios (HRs) for mortality for the unrestricted (i.e. no exclusion) analyses were 0.88 (95% Confidence Interval [CI] 0.84, 0.91) for those within the BMI Overweight range and 0.95 (CI 0.85, 1.05) for those within the BMI Obese-1 range. Summary mortality risk

estimates for specific exclusions were either associated with a reduced risk or were not significantly different for both BMI ranges. There was a reversal of the mortality risk, with an increased mortality risk for analyses which had simultaneously excluded smokers, conditions associated with weight loss, early deaths and had used a referent group falling in the BMI range ≥20 to <25.0 kg/m^2. Summary mortality HRs were 1.08 (CI 1.03, 1.13) for the BMI Overweight range and 1.31 (CI 1.17, 1.47) for the BMI Obese-1 range.

Conclusions: This meta-analysis showed that the risks for mortality for the BMI defined Overweight range and BMI Obese-1 range were markedly altered with combined exclusions. For healthier non-smokers (exclusion of conditions associated with weight loss) aged ≥65 years the BMI Overweight range and BMI Obese-1 range were associated with an elevated risk for mortality relative to those within the BMI Normal range.

3.2. Introduction

As highlighted in **Chapter 1,** body mass index (BMI) is widely used in clinical practice and research settings as a surrogate for adiposity. The World Health Organization (WHO) have set BMI ranges to classify adults as BMI Normal (18.5-24.9 kg/m^2), BMI Overweight (25.0-29.9 kg/m^2), and BMI Obese (≥30 kg/m^2, with sub-divisions for classes of obesity) (World Health Organization, 2000). These BMI ranges, however, were derived predominately from studies including younger and middle aged adults (Janssen and Mark, 2007; Mathus-Vliegen, 2012). Between 1980 and 2013 the global prevalence of adults classified as Overweight or Obese has increased across the age range, and overall it has been estimated that the global prevalence has increased by 27.5% during this time frame (Ng *et al.*, 2014). Due to the ageing population and the substantial increase in the numbers of adults classified as BMI Overweight or BMI Obese, it is therefore of public health importance to establish the prognostic utility of the current BMI thresholds in later life, and whether estimates differ for subgroups of older adults.

Previous reports have shown that younger and middle aged adults within the BMI Obese range are at an increased risk for mortality compared to those within the BMI Normal range (Calle *et al.*, 1999; Adams *et al.*, 2006; Whitlock *et al.*, 2009). However, for older adults (aged ≥65 years) several analyses have shown that the BMI Obese-1 (30.0-34.9 kg/m^2) range is associated with reduced (Al Snih *et al.*, 2007) or a similar mortality risk to those within the BMI Normal range (Flegal *et al.*, 2005; Lang *et al.*, 2008). This finding has been termed the 'obesity paradox'. Similarly, it has been shown that persons within the BMI Overweight range have a reduced (Al Snih *et al.*, 2007; Flicker *et al.*, 2010) or a similar (i.e. not significantly different) risk for mortality (Ajani *et al.*, 2004; Flegal *et al.*, 2005; Lang *et al.*, 2008) to those within the BMI Normal range.

Several meta-analyses have summarised the association between BMI and mortality for older adults (**Chapter 1**). Janssen and Mark (2007) reported that the mortality risk for those within the BMI Overweight range was not significantly different to those within the BMI Normal range, for persons within the BMI Obese-1 range there was a 10% increased risk (95% CI 1.06, 1.13) (Janssen and Mark,

2007). However, Flegal *et al*., (2013) reported that persons within the BMI Overweight range had reduced mortality risks relative to those within the BMI Normal range, whilst persons classified as BMI Obese-1 were not significantly different (Flegal *et al*., 2013). Moreover, Winter *et al*., (2014) showed increased mortality risks for those with BMI values <23 kg/m^2 and >33kg/m^2 relative to those within the BMI range 23.0-23.9 kg/m^2 (Winter *et al*., 2014).

As outlined in **Chapter 1** there are several possible contributors to the emergence of the obesity paradox in later life including the inclusion of smokers, inclusion of persons with conditions associated with weight loss, and the choice of the referent BMI group. Although Janssen and Mark (2007) and Winter et al., (2014) reported estimates for subgroups, i.e. exclusion of current smokers, no estimates were provided for combined subgroups (Janssen and Mark, 2007; Winter *et al*., 2014). Excluding one subgroup only (e.g. smokers) may still distort the mortality risk estimates as other subgroups (e.g. those with conditions associated with weight loss) remain within the analysis cohort.

In this chapter I summarise cohort studies that have reported on the association between BMI and mortality for adults aged ≥65 years. Only studies with mortality risk estimates for the BMI Overweight range and/or BMI Obese-1 range and with the referent group consisting of BMI values within the BMI Normal range were included. In this chapter I focus on the effect of both the individual (e.g. specific) and combined exclusions of subgroups (smokers, early deaths, conditions associated with weight loss) on the obesity paradox with consideration of the BMI referent group using a meta-analysis approach.

3.3. Methods

3.3.1. Data sources

This review includes articles that reported risk estimates for adults aged ≥65 years for the BMI Overweight and/or BMI Obese-1 ranges with all-cause mortality. Publications were identified by searching Embase, Medline, and Scopus electronic databases up to 13th August 2016. Search terms included "body mass index" or "obesity" or "overweight"; "mortality" or "deaths"; "aged, 65 and over" or "elderly" or "aged, 80 and over" or "aged" or "geriatrics"; or "prospective" or "cohort"; "hazard ratio(s)" or "relative risk(s)" or "rate ratio(s)". These were subsequently limited to English language articles published since 1st January 2000 as mortality risks may be altered with changing treatment patterns for other cardiovascular risk factors (e.g. high blood pressure). Publications were also identified from previous systematic reviews and meta-analyses.

3.3.2. Study selection

Inclusion criteria consisted of cohort studies with a minimum of 3 years of follow-up, subjects aged ≥65 years, minimum of 1,000 subjects within each subgroup, risk estimates reported for the BMI Overweight and/or BMI Obese-1 range, all-cause mortality as the outcome, and with the referent group consisting of BMI values within the BMI Normal range. Studies were excluded which comprised of nursing home residents only, populations with specific medical conditions/diagnoses (e.g. frailty), and wholly non-Caucasian populations. Publications which presented mortality risk estimates in figure form were also excluded. Publications which used the same cohort were included if mortality risk estimates were reported for different subgroups. Articles which were excluded are presented in the supplementary material Table S3.1.

3.3.3. Data extraction

The following were extracted from each publication: surname of the first author, year of publication, study name, baseline year(s), number of subjects, age range, gender, exclusion criteria, follow-up period, number of deaths, model adjustments, BMI groups, method of obtaining height and weight, and reported mortality risk estimates. Mortality risk estimates were extracted from the most

complex model unless it included adjustments for intermediate variables along the causal pathway (e.g. cholesterol, diabetes, or hypertension), in which an alternative model was used. However, if the alternative model was adjusted for age only then the most complex model was used.

3.3.4. Statistical analysis

A fixed-effects model was used to determine overall mortality risk estimates for individual studies which reported estimates separately by gender or age group (supplementary material tables S3.2 and S3.3). A random-effects model was used to combine the estimates from the individual studies. The I^2 statistic was used to assess the degree of heterogeneity. Summary mortality risk estimates were derived for the BMI Overweight range and the Obese-1 range relative to those within the BMI Normal range. Estimates were summarised for the following:

- analyses with no restrictions (unrestricted)
- analyses excluding smokers only
- analyses excluding early deaths only
- analyses excluding conditions associated with weight loss only
- analyses excluding smokers and early deaths
- analyses excluding smokers and conditions associated with weight loss
- analyses excluding early deaths and conditions associated with weight loss
- analyses excluding smokers, early deaths, and conditions associated with weight loss.

Estimates were also summarised for studies using either the whole of the conventional BMI Normal range (18.5 to 24.9 kg/m^2) or where the referent group fell within the BMI range ≥20 to <25.0 kg/m^2. For this analysis, I used R version 3.2.0 with the packages ("metafor" version 1.9-9).

3.4. Results

3.4.1. Characteristics of the studies

A total of 40 articles were included in this review (see supplementary material figure S3.1). Study characteristics and the reported mortality risk estimates for unrestricted analyses (no restrictions) and restricted analyses (e.g. exclusion of smokers) are presented in **Table 3.1** and **Table 3.2** respectively**.** Most studies were conducted in the United States of America or Europe, had ≥10 years of follow-up, and had baseline periods before 1st January 2000. Four studies had a baseline period in the 21st century only. Reported sample sizes ranged from 1,000 to 28,466 participants. Eighteen studies used the conventional BMI Normal range and fourteen studies used a BMI group of ≥20.0 kg/m^2 (≥20.0 to <25.0 kg/m^2) for the referent. Nineteen studies had a lower age boundary of 65 years. Most studies included broad age ranges of >10 years.

Table 3.1 | Unrestricted analyses (no exclusion of smokers or conditions associated with weight loss or exclusion of early deaths) of BMI groups within the Overweight (25.0-29.9 kg/m^2) and Obese-1 (30.0-34.9 kg/m^2) range with mortality for adults aged ≥65 years with at least ≥1000 subjects

Study; baseline year(s) (Author, year)	**Subjects**	**Exclusion criteria[1]/ restriction**	**Follow up; (deaths)**	**Model adjustments**	**BMI groups [method]**	**Results**
NIH-AARP 1995-1996 (Adams *et al.*, 2006)	66-71 y - M & W	Proxy response	10 y [max] (20,018 M & 8,482 W)	Age, ethnicity, education, smoking status, PA, & alcohol intake	M 23.5-24.9 M 25.0-26.4 M 26.5-27.9 M 28.0-29.9 M 30.0-34.9 W 23.5-24.9 W 25.0-26.4 W 26.5-27.9 W 28.0-29.9 W 30.0-34.9 [self-report]	1.00 0.91 (0.87, 0.96) 0.95 (0.90, 1.00) 0.96 (0.91, 1.01) 1.05 (0.99, 1.10) 1.00 1.01 (0.92, 1.10) 1.04 (0.95, 1.14) 1.06 (0.97, 1.16) 1.14 (1.05, 1.23)
EPESE 1982-1983; 1986;1993 (Al Snih *et al.*, 2007)	≥65 y 12,725 M & W	ADL limitations	7 y [max] (3,122)	Age, gender, marital status, smoking status, formal education, comorbidity (cancer, HTN, DM, hip fracture, heart attack or stroke), & site	18.5-24.9 25.0-29.9 30.0-34.9 [4 self-report; 1 measured]	1.00 0.78 (0.72, 0.85) 0.80 (0.72, 0.90)
MELSHA 1994 (Atlantis, Browning and Kendig, 2004)	≥65 y 1,000 M & W	Institutionalized, inhabiting non-private accommodation, or not able to speak basic English	12 y [max] (409)	Age, gender, current smoker, IADL dependent, timed 'get up and go', social activity, cognitive impairment, & CVD	18.5-24.9 25.0-29.9 [measured]	1.00 0.96 (0.77, 1.20)

Table 3.1 continued

Study; baseline year(s) (Author, year)	**Subjects**	**Exclusion criteria[1]/ restriction**	**Follow up; (deaths)**	**Model adjustments**	**BMI groups [method]**	**Results**
PAQUID - (Berraho *et al.*, 2010)	≥65 y 3,646 M & W		13 y [max] (1,973)	Age, gender, physical activities, smoking status, & comorbidity (DM, dyspnea, HTN, IHD, stroke & no. of medications)	22.0-24.9 25.0-29.9 [self-report]	1.00 0.98 (0.88, 1.10)
NHANES III 1988-1994 (Borrell and Samuel, 2014)	≥65 y (16.9% of 16,868) M & W	Ethnicity as “other”	14.25 p-y [median]	Age, gender, ethnicity, education, smoking, & LTPA	18.5-24.9 25.0-29.9 30.0-34.9 [measured]	1.00 0.89 (0.80, 0.99) 0.92 (0.78, 1.08)
GRAS 2001-2004 (Cheng *et al.*, 2016)	66.8-93.9 y 4,565 M & W	Height <111.8 cm or >228.6 cm, weight <24.9 kg or >453.6 kg, or BMI <12 or >70	14.4 y [max] (2,306)	Age, gender, smoking, & alcohol drinker	18.5-24.9 25.0-29.9 30.0-34.9 [measured]	1.00 0.84 (0.75, 0.94) 0.91 (0.80, 1.03)
Leisure World Cohort Study 1981-1985 (Corrada *et al.*, 2006)	≥80 y 2,777 M & W		23 y [max] (2,762)	Gender & smoking status	18.5-24.9 25.0-29.9 [self-report]	1.00 0.89 (0.81, 0.98)

Table 3.1 continued

Study; baseline year(s) (Author, year)	Subjects	Exclusion criteria[1]/ restriction	Follow up; (deaths)	Model adjustments	BMI groups [method]	Results
SENECA 1988-1989 (de Hollander *et al.*, 2012 b)	70-75 y 1,970 M & W	Living in a psychogeriatric nursing home, unable to fluently speak the country's language & unable to answer questions without assistance	10 y [max] (751)	Age, gender, education, & smoking	20.0-25.0 25.0-30.0 [measured]	1.00 0.92 (0.78,1.09)
Study of Osteoporotic Fractures 1986-1988; visit 2 measures taken at 1989-1991 (Dolan *et al.*, 2007)	≥67 y by visit 2 8,029 W	Those with bilateral hip replacements and those unable to walk without assistance.	8 y [max] (945)	Age, smoking, self-reported health, grip strength, nonthiazide diuretic use, & femoral neck BMD	≤22.38 >26.73-29.82 [measured]	1.00 0.72 (0.58, 0.89)
ALSWH 1996 (Ford, Spallek and Dobson, 2008)	70-75 y 12,422 W		Through to 31 Oct 2005 (2,321)	Age, self-rated health, exercise, smoking status, co-morbidity score, & marital status	18.5-24.9 25.0-29.9 [self-report]	1.00 0.84 (0.74, 0.95)

Table 3.1 continued

Study; baseline year(s) (Author, year)	Subjects	Exclusion criteria[1]/ restriction	Follow up; (deaths)	Model adjustments	BMI groups [method]	Results
CHAMP 2005-2007 (Hirani *et al.*, 2014)	70-97 y 1,508 M (with all values)	Living in a residential aged care facility	8.2 y [max] (461)	Age, smoking status, alcohol intake, MI, CHF, cancer, WBC count, depressive symptoms, IADL disability, ADL disability, chair stands & HGB albumin	20.0-24.9 25.0-29.9 [measured]	1.00 0.70 (0.55, 0.90)
Oslo cohort of men 2000 (Holme and Tonstad, 2015)	68-77 y, 5,239 M	No CVDs, HTN / DM in 1972–73 or BMI <18.5	11 y [max] (2,145)	Age, y of education, smoking, DM, MI, antihypertensive use, cholesterol-lowering use, & cerebrovascular disease	22.0-24.9 25.0-27.4 27.5-29.9 30.0-34.9 [measured]	1.00 0.91 (0.78, 1.00) 0.86 (0.76, 0.98) 1.15 (0.99, 1.33)
CHS 1989-1990 (Janssen, 2007)	≥65 y 4,968 M & W	Institutionalized, required proxy respondent & BMI <18.5	9 y [max] (1,464)	Age, gender, ethnicity, SES, smoking, & PA	20.0-24.9 25.0-29.9 [measured]	1.00 0.92 (0.82, 1.03)
FHS 1948 (merged 24 examinations) (Janssen and Bacon, 2008)	≥70 y 3,238 M & W		10.7 y [median] (2,160)	Age, gender, smoking, alcohol, & exam cycle of BMI assessment at age 70	<25.0 25.0-29.9 [measured]	1.00 0.99 (0.89, 1.09)

Table 3.1 continued

Study; baseline year(s) (Author, year)	Subjects	Exclusion criteria[1]/ restriction	Follow up; (deaths)	Model adjustments	BMI groups [method]	Results
AGES-Reykjavik Study 2002-2006 (Koster *et al.*, 2015)	66-96 y 2,900 W	BMI <18.5	11 y [max] (882)	Age, education, smoking status, PA, & alcohol intake	18.5-24.9 25.0-29.9 [measured]	1.00 0.80 (0.68, 0.93)
NLTCS data 1994 (Kulminski *et al.*, 2008)	≥65 y 4,791 M & W		9 y [max] (2,956)	Age, gender, smoking, drinking, heart attack, other heart problems, stroke, cancer, ethnicity, & change in weight	22.0-24.9 25.0-29.9 30.0-34.9 [self-report]	1.00 0.82 (0.74, 0.91) 0.78 (0.68, 0.91)
Medicare recipients in New York City 1992-1994 (Luchsinger *et al.*, 2008)	≥65 y 1,372 M & W		9,974 person-years [through to 2003] (479)	Age, gender, education, ethnicity, cancer, current smoking, & dementia	18.5-24.9 25.0-29.9 [measured]	1.00 0.80 (0.70 ,0.90)
WHI OS 1993 (McTigue *et al.*, 2006)	70-79 y 18,651 White W	BMI <18.5	9.9 y [max] (1,876)	Age, tobacco use, education, US region, & PA	18.5-24.9 25.0-29.9 30.0-34.9 [measured height]	1.00 0.86 (0.77, 0.96) 1.00 (0.87, 1.15)

Table 3.1 continued

Study; baseline year(s) (Author, year)	Subjects	Exclusion criteria[1]/ restriction	Follow up; (deaths)	Model adjustments	BMI groups [method]	Results
ALSA 1992/1993 (Miller *et al.*, 2002)	≥70 y 1,396 M & W		8 y [max] (41.5%)	Age, gender, marital status, smoking, self-rated health, assistance in ADLs, comorbidity, cognition performance, & depression	20.0-25.0 >25.0-30.0 [measured]	1.00 0.99 (0.82, 1.21)
SALLS 1988-1989 (Sundquist *et al.*, 2004)	≥65 y 1,414 M & 1,792 W	Institutionalized & proxy responses	12.0 y [max] (881 M & 925 W)	Age, gender, education, PA, smoking habits, & self-rated health	18.6-24.9 25.0-29.9 [self-report]	1.00 0.87 (0.78, 0.96)

[1] except missing variables

For terms which have been abbreviated see List of abbreviations Table. For studies which have been abbreviated see List of studies abbreviations Table. M: Men and W: Women

Table 3.2 | Restricted analyses (in terms of smoking and conditions associated with weight loss or exclusion of early follow-up period) of BMI groups within the Overweight (25-29.9 kg/m^2) and Obese-1 (30-34.9 kg/m^2) range with mortality for adults aged ≥65 years with ≥1000 subjects

Study; baseline year(s) (Author, year)	**Subjects**	**Exclusion criteria[1]/ restriction**	**Follow up; (deaths)**	**Model adjustments**	**BMI groups [method]**	**Results**
HPFS 1986 (Baik *et al.*, 2000)	≥65 y - M (3,940 with waist measures)	MI, angina, stroke, cancer[2] CABG/ angioplasty, transient cerebral ischemia, peripheral venous thrombosis, intermittent claudication, pulmonary embolus, paroxysmal atrial tachycardia, other heart-rhythm disturbances, chronic RF, chronic pulmonary disease & BMI <15 or >50. First four years excluded & without weight loss ≥10 pounds in the prior 5 years	10 y [max] (272)	Age, smoking status (cigs/day), FH MI/ colon cancer < 60 y, profession, marital status, height, alcohol intake, quintiles of calorie-adjusted intakes of vitamin A, vitamin E, & dietary fiber	<23.0 25.0-26.9 27.0-29.9 [self-report]	1.00 0.75 (0.53, 1.08) 0.83 (0.56, 1.23)

Table 3.2 continued

Study; baseline year(s) (Author, year)	Subjects	Exclusion criteria[1]/ restriction	Follow up; (deaths)	Model adjustments	BMI groups [method]	Results
WHI 1993-1998 (Bea *et al.*, 2015)	70-79 y 1,752 W	Deaths within first 2 y	13.6 y [mean; SD 4.6 y] (591)	Age, age at menopause, PA, diet quality, ethnicity, pack-y of smoking, alcohol intake, hormone use, & CT arm	18.5-24.9 25.0-29.9 30.0-34.9 [measured]	1.00 1.01 (0.83, 1.23) 1.02 (0.80, 1.30)
19 PCS [3] 1976-2002 (Berrington de Gonzalez *et al.*, 2010)	70-84 y ~28,466 [4] M & W	BMI < 15 or ≥50 & <1 y of follow up. Restricted to never smokers, no cancer/HD	10 y [median; range 5 to 28y] (5,160)	Age, gender, alcohol intake, education, marital status, PA, & study	22.5-24.9 25.0- 27.4 27.5-29.9 30.0-34.9 [18 self-report]	1.00 1.04 (0.96, 1.13) 1.15 (1.04, 1.26) 1.24 (1.12, 1.38)
EPIDOS 1992-1993 (Blain *et al.*, 2010)	≥75 y 1,300 W	Walking with a cane, unable to attend clinical center without assistance, unable to perform functional tests & respond to questionnaire, had a bilateral hip replacement/ suffered a hip fracture, Paget's disease of bone, ….	8 y [max] (410)	Age	18.0-25.0 25.0-30.0 [measured]	1.00 0.88 (0.71, 1.09)

Table 3.2 continued

Study; baseline year(s) (Author, year)	**Subjects**	**Exclusion criteria[1]/ restriction**	**Follow up; (deaths)**	**Model adjustments**	***BMI groups [method]***	***Results***
(Blain, 2010) continued		malignant bone disease, renal failure, hyperthyroidism/ treated hypothyroidism deaths first year				
GRAS 2001-2004 (Cheng *et al.*, 2016)	66.8-93.9 y M & W	Height <111.8 cm or >228.6 cm, weight <24.9 kg or >453.6 kg, or BMI <12 or >70.	10.9 y [mean; SD 3.8y]	Age, sex, alcohol drinker, blood glucose, diabetic medication, triglycerides, HDL cholesterol, LDL cholesterol, hypercholesterolemia medication, SBP, DBP, hypertension medication, & disease burden	0 disease burden [5] (*n* = 1152 & 292 deaths) 18.5-24.9 25.0-29.9 30.0-34.9 Never smokers (*n* = 2590 & 1093 deaths) 18.5-24.9 25.0-29.9 30.0-34.9 ….	 1.00 0.85 (0.62, 1.16) 0.97 (0.68, 1.38) 1.00 0.91 (0.77,1.08) 0.85 (0.70,1.03)

Table 3.2 continued

Study; baseline year(s) (Author, year)	Subjects	Exclusion criteria[1]/ restriction	Follow up; (deaths)	Model adjustments	BMI groups [method]	Results
(Cheng, 2016) continued					Exclusion never smokers and first five years (*n* = 2,371) 18.5-24.9 25.0-29.9 30.0-34.9 [measured]	 1.00 0.89 (0.73,1.08) 0.85 (0.68, 1.05)
Gerontological & geriatric studies in Gothenburg, 1971-1981 (Dey *et al.*, 2001)	≥70 y 1,133 M & 1,272 W	Cancer ≤ 70 y & BMI > 40	15 y [max] (781 M & 552 W)	Birth cohort & smoking habits	M 24.7- 26.4 M 26.5- 28.5 W 24.6-26.5 W 26.6-29.2 Exclusion deaths first 5 y (*n* = 1154 W included) W 24.7-26.7 W 26.8-29.2 [measured]	1.00 1.01 (0.81, 1.26) 1.00 1.16 (0.88, 1.52) 1.00 1.29 (0.90, 1.85)

Table 3.2 continued

Study; baseline year(s) (Author, year)	Subjects	Exclusion criteria[1]/ restriction	Follow up; (deaths)	Model adjustments	BMI groups [method]	Results
Study of Osteoporotic Fractures 1986-1988; visit 2 measures taken at 1989-1991 (Dolan *et al.*, 2007)	≥67 y by visit 2 4,864 [6] W	Those with bilateral hip replacements and unable to walk with assistance Restricted to never smokers	8 y [max] (457) [6]	Age, smoking, self-reported health, grip strength, nonthiazide diuretic use, & femoral neck BMD	≤22.38 > 26.73–29.82 [measured]	1.00 0.81 (0.60, 1.09)
Nord-Trøndelag Health Study 1984-1986 (Ellekjaer, Holmen and Vatten, 2001)	≥70 y 3,034 M & 31,23 W (with BMI)	CHD/stroke/DM & BP medication use	10 y [max] (1,633 M & 1,223 W)	Age, current smoking, & SBP	M ≤22.95 M 25.11-27.35 W ≤23.23 W 25.98-29.00 [measured]	1.00 0.80 (0.69, 0.93) 1.00 0.62 (0.52, 0.75)
USRT Study 1983-1989 (Freedman *et al.*, 2006)	≥65 y 1,047 M & 3,525	Cancer[2]/ MI. Restricted to never smokers	7 person years(M) & 6 person-years (W) [Average; through to 2002] (887 M & 1,370 W[7])	Age, ethnicity, education, alcohol intake, & y first worked as a radiologic technologist	M 18.5-24.9 M 25.0-29.9 M 30.0-34.9 W 18.5-24.9 W 25.0-29.9 W 30.0-34.9 [self-report]	1.00 0.77 (0.57, 1.03) 1.15 (0.70, 1.89) 1.00 1.09 (0.89, 1.33) 1.44 (1.08, 1.92)

Table 3.2 continued

Study; baseline year(s) (Author, year)	Subjects	Exclusion criteria[1]/ restriction	Follow up; (deaths)	Model adjustments	BMI groups [method]	Results
Geneva University: Switzerland; 1990-2011 (Graf *et al.*, 2015)	≥65 y 1,726 M & 1,455 W	Resident outside of Switzerland, deaths within 1 month, negative FM & invalidated BIA measures	6.2 y [mean; SD 6.2 y] (1,007 M & 766 W)	Age, smoking, ambulatory/ hospitalized state, & calendar time	M 18.5-24.9 M 25.0-29.9 M 30.0-34.9 W 18.5-24.9 W 25.0-29.9 W 30.0-34.9 [measured]	1.00 0.76 (0.66, 0.88) 0.53 (0.40, 0.70) 1.00 0.89 (0.74, 1.07) 1.02 (0.80, 1.30)
NHANES I-III 1971-1975; 1976-1980; 1988-1994 (Greenberg, 2013)	65-74 y (2,144 Over-weight or Obese) M & W	Restricted to never smokers & without heart attack/stroke/cancer	15 y [max] (507 Over-weight and 374 Obese)	Age, gender, ethnicity, alcohol intake, history of serious illness smoking status, & cohort	23.0-24.9 25.0-29.9 [measured]	1.00 0.92 (0.74, 1.16)
NHIS 1997-2002 (Jackson *et al.*, 2014)	65-74 y 4,571 M & W	Born outside US, cancer/HD, BMI < 15 or > 55, DM diagnosed at < 25 y & treated with insulin. Restricted to never smokers & no DM	9 y [max]	Age, marital status, smoking status, LTPA, alcohol intake, poor income, region of country, & self-reported health status	18.5-24.9 25.0-29.9 30.0-34.9 [self-report]	1.00 0.45 (0.18, 1.14) 0.88 (0.39, 1.94)

Table 3.2 continued

Study; baseline year(s) (Author, year)	Subjects	Exclusion criteria[1]/ restriction	Follow up; (deaths)	Model adjustments	BMI groups [method]	Results
CHS 1989-1990 (Janssen, 2007)	≥65 y 2,495 M & W	Institutionalized, required proxy respondent & BMI <18.5 kg/m^2. Restricted to none/ passive smoking exposure	9 y [max]	Age, gender, ethnicity, SES, smoking, & PA	20.0-24.9 25.0-29.9	1.00 0.82 (0.69, 0.98)
NLTCS data 1994 (Kulminski *et al.*, 2008)	≥65 y (4,119 before exclusion of proxy reports [roughly 28%]) M & W	Restricted to never smokers and no reported cancer.	9 y [max]	Age, gender, smoking, drinking, heart attack, other heart problems, stroke, cancer, ethnicity, & change in weight	22.0-24.9 25.0-29.9 30.0-34.9	1.00 0.82 (0.71, 0.94) 0.84 (0.70, 1.02)
NHIS (US) 1987–1995 (except 1989) (Ma *et al.*, 2013)	65-99 y (17.4% of total never smokers population 106,964) M & W	Those who reported "fair"/ "bad" health, BMI < 15 or ≥100. Restricted to never smokers	16 y [median; through to 2006] (11,225 never smokers)	Age, gender, education, & ethnicity	18.5-24.9 25.0-29.9 30.0-34.9 Exclusion 5 y 18.5-24.9 25.0-29.9 30.0-34.9 [self-report]	1.00 0.97 (0.93, 1.02) 1.11 (1.03, 1.20) 1.00 0.99 (0.93, 1.04) 1.11 (1.02, 1.21)

Table 3.2 continued

Study; baseline year(s) (Author, year)	Subjects	Exclusion criteria[1]/ restriction	Follow up; (deaths)	Model adjustments	BMI groups [method]	Results
BCDDP follow-up study 1987 (Moore *et al.*, 2008)	≥65 y - W	BMI < 15 or >60 (BMI derived 10 y < start of FU)	10 y [max] (1,717)	Age, menopausal hormone use, annual household income, education, ethnicity, smoking (& cigs/day), & PA	21.0-23.4 25.0-27.4 27.5-29.9 30.0-34.9 [measured]	1.00 1.17 (1.02, 1.34) 1.01 (0.84, 1.21) 1.34 (1.10, 1.63)
Multiethnic Cohort Study 1993-1996 (Park *et al.*, 2012)	65-74 y - M & W	Cancer/ HD, those who had ever smoked, BMI <15 or >50 & deaths first 3 y	12.5 y [average] (1,660 M & 3,094 W)	Age & alcohol intake	M 23.0-24.9 M 25.0-27.4 M 27.5-29.9 M 30.0-34.9 W 23.0-24.9 W 25.0-27.4 W 27.5-29.9 W 30.0-34.9 [self-report]	1.00 1.03 (0.89, 1.18) 1.23 (1.04, 1.46) 1.46 (1.21, 1.75) 1.00 1.03 (0.92, 1.17) 1.11 (0.97, 1.27) 1.36 (1.19, 1.55)
Cancer Prevention Study II 1982 (Patel, Hildebrand and Gapstur, 2014)	≥70 y - M & W	99.9th % height/ weight, BMI <15, neither Black/White cancer[2], HD, stroke, chronic bronchitis, emphysema, asthma, currently ill, weight loss of ≥10 lbs past y. Restricted to never smokers	28 y [max] (8,455 M & 26,476 W)	Age, ethnicity, education, PA, alcohol use, marital status, aspirin use, fat intake, vegetable intake, & postmenopausal estrogen use (women)	M 22.5-24.9 M 25.0-27.4 M 27.5-29.9 M 30.0-34.9 W 22.5-24.9 W 25.0-27.4 W 27.5-29.9 W 30.0-34.9 [self-report]	1.00 1.00 (0.94, 1.05) 1.08 (1.01, 1.16) 1.06 (0.95, 1.17) 1.00 1.02 (0.99, 1.06) 1.07 (1.02, 1.12) 1.13 (1.08, 1.19)

Table 3.2 continued

Study; baseline year(s) (Author, year)	Subjects	Exclusion criteria[1]/ restriction	Follow up; (deaths)	Model adjustments	BMI groups [method]	Results
53 family practices UK (Price *et al.*, 2006)	≥75 y 3,994 M & 6,536 W	Long term nursing institution & terminally ill. Restricted to non-smokers	5.9 y [median; through to Septem-ber 2002] (1,874 M & 2,480 W)	Age, height, serious illness in loved one within past y, alcohol intake, depression, cognitive impairment, unexplained recent weight loss >3.2 kg, housing type, UK quintiles of Carstairs area deprivation score, & former smoking	M 15.9-23.0 M >25.0-26.7 M >26.7-29.0 W 14.7-22.3 W 26.8-29.7 [measured]	1.00 0.77 (0.67, 0.88) 0.73 (0.63, 0.85) 1.00 0.76 (0.67, 0.87)
RAND Health and Retirement Survey (HRS) 1992 - 1993 (Reuser, Bonneux and Willekens, 2008)	≥80y - M & W	BMI <18.5 Events and outcomes [counted from three years]	10.8 y [max]	Age, education, & smoking,	M 23.0-24.9 M 25.0-29.9 M 30.0-34.9 W 23.0-24.9 W 25.0-29.9 W 30.0-34.9 [self-report]	1.00 0.86 (0.70, 1.06) 0.85 (0.60, 1.21) 1.00 0.80 (0.66, 0.98) 0.95 (0.72 ,1.26)
Multiphase HE Finland 1973-1977 (Visscher *et al.*, 2004)	≥65 y 1,221 in BMI analysis W	Restricted to never smokers	15 y [max] (583)	Age, educational, geographic region, & alcohol use	18.5-24.9 25.0-29.9 [measured]	1.00 0.9 (0.7, 1.1)

Table 3.2 continued

Study; baseline year(s) (Author, year)	Subjects	Exclusion criteria[1]/ restriction	Follow - up; (deaths)	Model adjustments	BMI groups [method]	Results
Medicare Current Beneficiary Surveys, linked to Medicare enrolment files 1994-2000 (Wee, 2011)	≥65 y 20975 (8,425 M & 11,583 W included in BMI mortality analysis)	Died within first 12 months & those with HIV/AIDS (*n* =15 with HIV/AIDS)	14 y [max] (11,093 over the whole 14y)	Age, smoking status, education, proxy response, rheumatoid arthritis, cancer, cognitive impairment, & chronic lung disease	M 22.0-24.9 M 25.0-27.4 M 27.5-29.9 M 30.0-34.9 W 22.0-24.9 W 25.0-27.4 W 27.5-29.9 W 30.0-34.9 [self-report]	1.00 0.84 (0.78, 0.92) 0.81 (0.73, 0.90) 0.89 (0.81, 0.99) 1.00 0.90 (0.81, 0.99) 0.82 (0.74, 0.92) 0.98 (0.88, 1.08)
PLCO 1993-2001 (Xiao *et al.*, 2014)	65-78 y Non-Hispanic Black/ White - M & W	Neither non-Hispanic Black/White, BMI <15 or >50. Restricted to not current cigarette smokers/ recent quitters, no cancer/heart attack/ stroke & BMI 20-50	13 y [mean; through to 2009] (3,080 M, & 1,932 W)	Age, education, marital status, remote former smoking, previous pack-years, & y since quitting smoking	White M 20.0-24.9 25.0-29.9 30.0-34.9 White W 20.0-24.9 25.0-29.9 30.0-34.9 [self-report]	 1.00 1.06 (0.98, 1.16) 1.31 (1.17, 1.46) 1.00 1.03 (0.93, 1.15) 1.26 (1.10, 1.43)
PHS 1981-1984 (Yates, Djousse and Kurth, 2013)	66-84 y 2,280 M (for multivar-iate analysis)	History of cancer [2] /MI/ transient cerebral ischemia/ stroke/ other serious disease	25 y [max] (1,387 overall out of 2,357)	Age, smoking status, alcohol intake, exercise frequency, HTN, DM, hypercholesterolemia, angina, & treatment assignment	<25.0 25.0-29.9 [self-report]	1.00 0.97 (0.86, 1.08)

Notes for Table 3.2

[1] except missing variables

[2] except non-melanoma skin cancer

[3] AARP, AHS-1, AHS, BCDDP, CTS, CLUE, COSM, HFPS, IWHS, MCCS, NHS, NYUWHS, PHS, PLCO, SMC, USRT, VITAL, WHS, WLHS

[4] number reported by Winter *et al*., (2014) (Winter *et al.*, 2014)

[5] based on Charlson Index

[6] number reported by Aune *et al*., (2016) (Aune *et al.*, 2016)

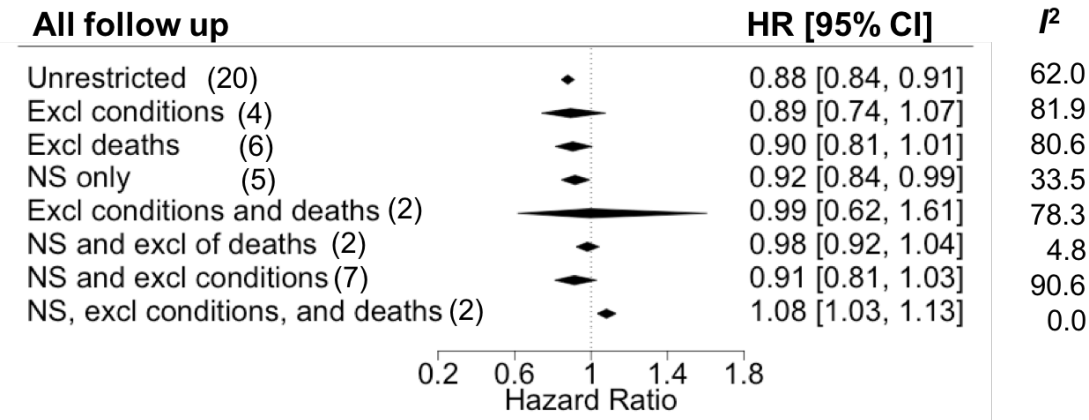
[7] number of deaths for males and females aged ≥65 years

For terms which have been abbreviated see List of abbreviations Table. For studies which have been abbreviated see List of Studies abbreviations Table.

3.4.2. BMI Overweight range and mortality

Forty studies reported mortality risk estimates for the BMI Overweight range. **Figure 3.1** shows the summary mortality hazard ratios (HR) for the BMI Overweight range relative to studies which used referent groups falling anywhere within the BMI Normal range for unrestricted (no exclusion) analyses, specific exclusions (e.g. never smokers only) and combined exclusions. For the BMI defined Overweight range there were reduced mortality risks for analyses which were considered unrestricted (summary HR 0.88 95% CI 0.84, 0.91) and for analyses which excluded never smokers only (summary HR 0.92 95% CI 0.84, 0.99). There were increased mortality risks for the BMI Overweight range for analyses which simultaneously excluded never smokers, early deaths, and conditions associated with weight loss (HR 1.08 CI 1.03, 1.13, with low heterogeneity I^2 0.0%) relative to those within the BMI Normal range. The mortality risks for the BMI Overweight range were not significantly different to those within the BMI Normal range for the remaining analyses.

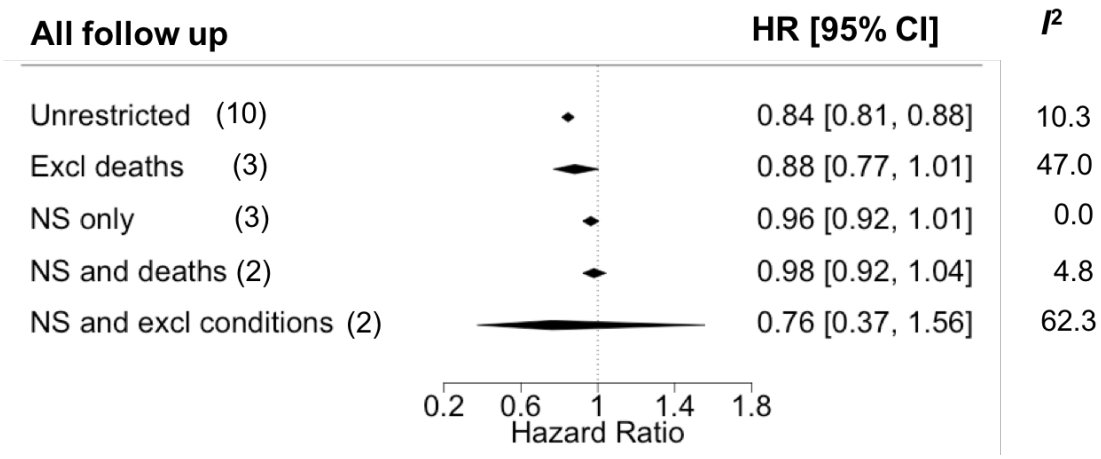
Figure 3.1 | Summary mortality risk estimates for the BMI Overweight range relative to studies which used a referent group falling anywhere within the BMI Normal range for unrestricted analyses, specific exclusions and combined exclusions



Note: Unrestricted refers to analyses which did not exclude smokers, conditions associated with weight loss or early deaths. Excl conditions refers to analyses which excluded conditions associated with weight loss. Excl deaths refers to analyses which excluded early deaths during the follow up. NS refers to analyses which were restricted to never/non-smokers. The number in brackets refers to the number of analyses included.

Summary mortality risk estimates for studies which used the whole of the conventional BMI Normal range as the referent group (18.5-24.9 kg/m^2) are presented in **Figure 3.2**. For analyses which used the whole of the conventional BMI Normal range there were reduced mortality risks for the BMI Overweight range for unrestricted analyses (summary HR 0.84 95% CI 0.81, 0.88, with low heterogeneity 10.3%). The mortality risks for the BMI Overweight range were not significantly different to the conventional BMI Normal range for analyses which excluded never smokers only or excluded both never smokers and early deaths, with lower heterogeneity reported compared to the unrestricted analyses. The remaining analyses had higher heterogeneity, with the summary mortality risk not being significantly different to the referent range.

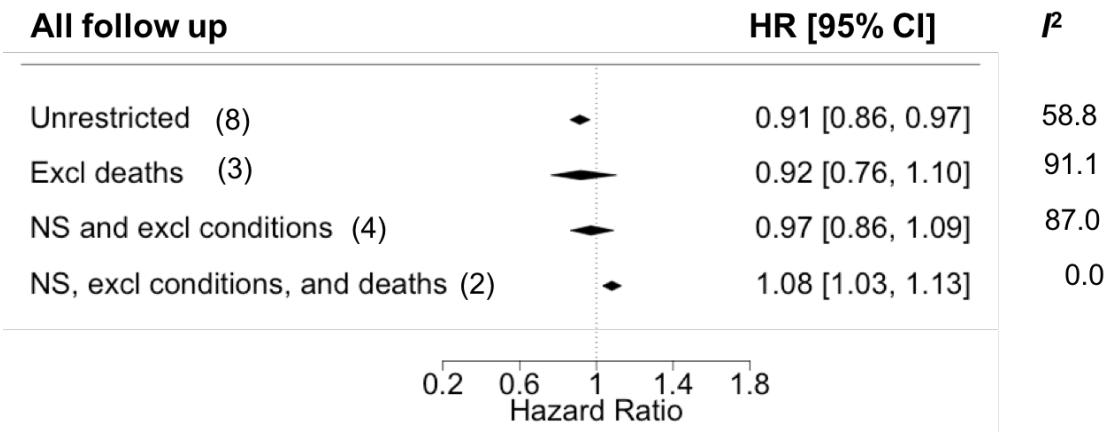
Figure 3.2 | Summary mortality risk estimates for the BMI Overweight range for studies which used the whole of the conventional BMI Normal range (18.5-24.9 kg/m^2) as the referent group for unrestricted analyses, specific exclusions and combined exclusions



Note: Unrestricted refers to analyses which did not exclude smokers, conditions associated with weight loss or early deaths. Excl conditions refers to analyses which excluded conditions associated with weight loss. Excl deaths refers to analyses which excluded early deaths during the follow up. NS refers to analyses which were restricted to never/non-smokers. The number in brackets refers to the number of analyses included. The number in brackets refers to the number of analyses included.

Summary mortality risk estimates for studies which had used a referent group falling in the BMI range ≥20 to <25.0 kg/m^2 are presented in **Figure 3.3**. The summary mortality risks for the BMI Overweight range were not significantly different for analyses which were unrestricted, excluded deaths only, or excluded both never smokers and conditions associated with weight loss. Increased mortality risks were reported for analyses which simultaneously excluded smokers, deaths, and conditions associated with weight loss with low heterogeneity.

Figure 3.3 | Summary mortality risk estimates for the BMI Overweight range relative to those which used a referent group falling within the BMI range ≥20.0 to 24.9 kg/m^2 for unrestricted analyses, specific exclusions and combined exclusions

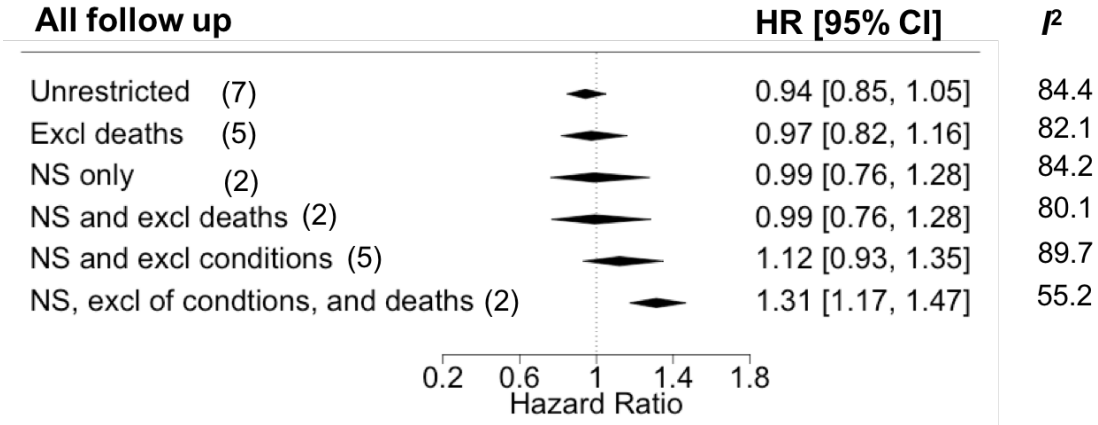


Note: Unrestricted refers to analyses which did not exclude smokers, conditions associated with weight loss or early deaths. Excl conditions refers to analyses which excluded conditions associated with weight loss. Excl deaths refers to analyses which excluded early deaths during the follow up. NS refers to analyses which were restricted to never/non-smokers. The number in brackets refers to the number of analyses included.

3.4.3. BMI Obese-1 range and mortality

Nineteen studies reported mortality risk estimates for the BMI Obese-1 range. **Figure 3.4** shows the summary mortality hazard ratios (HR) for the BMI Obese-1 range relative to studies which used referent groups falling anywhere within the BMI Normal range for unrestricted (no exclusion) analyses, specific exclusions (e.g. never smokers only) and combined exclusions. The summary mortality risks for the BMI Obese-1 range were not significantly different to those within the BMI Normal range for analyses which were unrestricted, had singular exclusions (e.g. never smokers), excluded both smokers and early deaths, and those which excluded both smokers and conditions associated with weight loss, all with larger heterogeneity. There were increased mortality risks for analyses which simultaneously excluded smokers, conditions associated with weight loss and early deaths (HR 1.31 95% CI 1.17, 1.47), with lower heterogeneity compared to the other analyses.

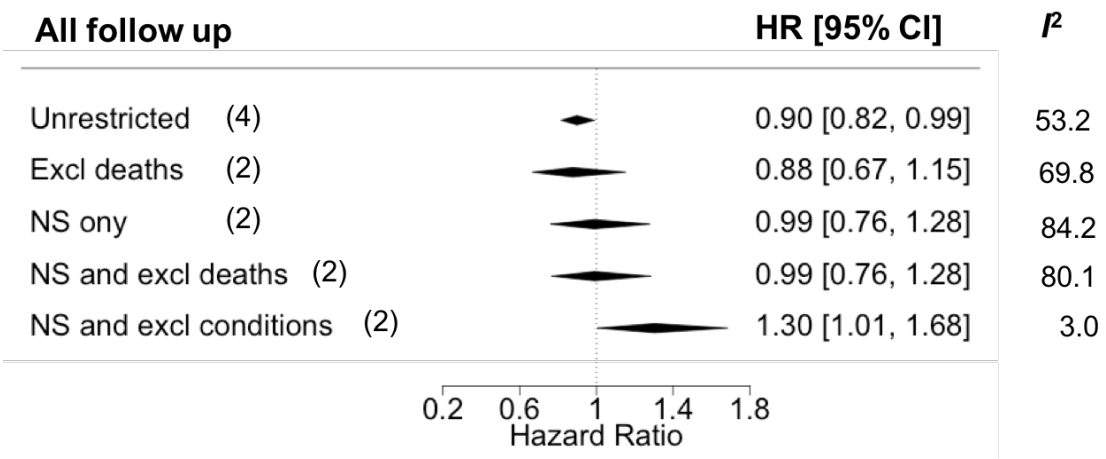
Figure 3.4 | Summary mortality risk estimates for the BMI Obese-1 range relative to studies which had used a referent group falling anywhere within the BMI Normal range for unrestricted analyses, specific exclusions and combined exclusions



Note: Unrestricted refers to analyses which did not exclude smokers, conditions associated with weight loss or excluding early deaths. Excl conditions refers to analyses which excluded conditions associated with weight loss. Excl deaths refers to analyses which excluded early deaths during the follow up. NS refers to analyses which were restricted to never/non-smokers. The number in brackets refers to the number of analyses included.

Summary mortality risk estimates for studies which used the whole of the conventional BMI Normal range as the referent group (18.5-24.9 kg/m^2) are presented in **Figure 3.5**. There were reduced mortality risks for those within the BMI Obese-1 range compared to those within the conventional BMI Normal range for unrestricted analyses (HR 0.90 CI 0.82, 0.99). There were increased mortality risks for analyses which excluded never smokers and conditions associated with weight loss with low heterogeneity. The remaining analyses, with large heterogeneity, showed that the mortality risks were not significantly different.

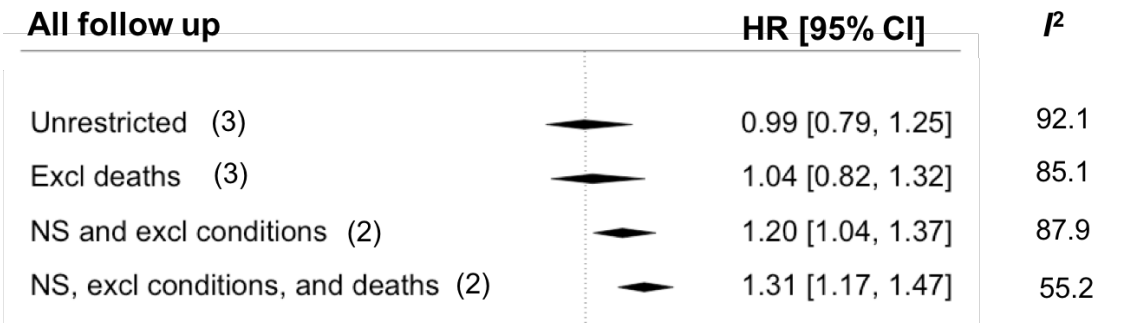
Figure 3.5 | Summary mortality risk estimates for the BMI Obese-1 range for studies which used the whole of the conventional BMI Normal range (18.5-24.9 kg/m^2) as the referent group for unrestricted analyses, specific exclusions and combined exclusions



Note: Unrestricted refers to analyses which did not exclude smokers, conditions associated with weight loss or excluding early deaths. Excl conditions refers to analyses which excluded conditions associated with weight loss. Excl deaths refers to analyses which excluded early deaths during the follow up. NS refers to analyses which were restricted to never/non-smokers. The number in brackets refers to the number of analyses included.

Summary mortality risk estimates for studies which had used a referent group falling within the BMI range ≥20.0 to 24.9 kg/m^2 are presented in **Figure 3.6**. The summary mortality risks for the BMI Obese-1 range were not significantly different for unrestricted analyses and analyses which excluded early deaths only, both with large heterogeneity. There were increased mortality risks for analyses which excluded both smokers and conditions associated with weight loss and analyses which simultaneously excluded smokers, early deaths, and conditions associated with weight loss.

Figure 3.6 | Summary mortality risk estimates for the BMI Obese-1 range relative to those which used a referent group falling within the BMI range ≥20.0 to 24.9 kg/m^2 for unrestricted analyses, specific exclusions and combined exclusions



Note: Unrestricted refers to analyses which did not exclude smokers, conditions associated with weight loss or excluding early deaths. Excl conditions refers to analyses which excluded conditions associated with weight loss. Excl deaths refers to analyses which excluded early deaths during the follow up. NS refers to analyses which were restricted to never/non-smokers. The number in brackets refers to the number of analyses included.

3.4.4. Sensitivity analyses

Several studies (Ellekjaer, Holmen and Vatten, 2001; Yates, Djousse and Kurth, 2013; Holme and Tonstad, 2015; Cheng *et al.*, 2016) adjusted for intermediates along the causal pathway (e.g. cholesterol, diabetes, or hypertension) between BMI and mortality. These were excluded from the unrestricted and subgroup analyses where possible (supplementary material table S3.4). The direction of the mortality association tended to be the same following the exclusion of these analyses. The mortality risk estimate, however, for the BMI Overweight range (HR 0.91 CI 0.82, 1.01) relative to those with a BMI within the Normal range became non-significant for the never smokers analysis overall after the exclusion of the analysis by Cheng *et al.*, (2016).

3.5. Discussion

The findings of this review and meta-analysis show that the mortality risks for the BMI Overweight range and BMI Obese-1 range are markedly altered with combined exclusions compared to specific exclusions or unrestricted analyses. There were reduced mortality risks for the BMI Overweight range for the unrestricted analyses relative to those within the BMI Normal range. Mortality risks were not significantly different in analyses which either singularly or jointly excluded deaths or conditions associated with weight loss. Risks were either reduced or not significantly different for analyses excluding smokers only or in combination with deaths or conditions associated with weight loss. However, for healthier non-smokers (e.g. exclusion of smokers, conditions associated with weight loss, and early deaths), there were increased mortality risks for those within the BMI Overweight range, with low heterogeneity.

For the BMI Obese-1 range, the summary mortality risk was reduced for analyses considered unrestricted and which had used the whole of the conventional BMI Normal range as the referent group, with large heterogeneity. The summary mortality risks for singular exclusions, and combinations of two exclusions were not significantly different to those within the BMI Normal range. The lowest heterogeneity was reported for analyses which used the whole of the conventional BMI Normal range as the referent group and had simultaneously excluded smokers and conditions associated with weight loss, conferring an increased mortality risk. There was also an increased mortality risk, with a similar point estimate, for analyses which simultaneously excluded smokers, early deaths, and conditions associated with weight loss.

From a public health perspective smokers, persons with conditions associated with weight loss and those who are relatively healthy may be managed differently in terms of weight control. Persons with conditions associated with weight loss (e.g. cancer, dementia, and heart failure) may be monitored for further weight loss and signs of malnutrition. Smokers considering smoking cessation may be advised on potential weight gain following complete cessation. Whilst for persons who are relatively healthy (e.g. with no apparent weight loss and not currently smoking), the focus may be more towards preventing weight gain and obesity. Interestingly, the summary mortality risks were elevated for the BMI Overweight

and BMI Obese-1 ranges for analyses which used all three exclusions and a BMI referent range with a lower bound of 20 kg/m^2 (Berrrington de Gonzalez et al., 2010 used the range 22.5-24.9 kg/m^2 and Park et al., 2012 used the range 23.0-24.9 kg/m^2).

3.5.1. Comparison to previous literature

Previous meta-analyses have reported that the mortality risk for adults aged ≥65 years within the BMI Overweight range is reduced (Flegal *et al.*, 2013; Winter *et al.*, 2014) or not significantly different (Janssen and Mark, 2007) to those within the BMI Normal range. It has been documented that the mortality risk for adults within the BMI Obese-1 range is either not significantly different (Flegal *et al.*, 2013) or is associated with a modest increased risk when compared to those within the BMI Normal range (Janssen and Mark, 2007). Winter *et al*., (2014) found increased mortality risks for those with BMI values >33.0kg/m^2 compared to those within the BMI range 23.0-23.9 kg/m^2 (Winter *et al.*, 2014). The meta-analysis I presented in this chapter showed reduced mortality risks for the BMI Overweight range and non-significant mortality risks for the BMI Obese-1 range relative to those within the BMI Normal range for analyses without restrictions. However, the results following all three combined exclusions contest the notion that those within the BMI Overweight and BMI Obese-1 ranges have improved survival compared to those within the BMI Normal range.

Several of the previous meta-analyses reported mortality risk estimates for the BMI Overweight and BMI Obese-1 ranges for adults aged ≥65 years using subgroups (e.g. never smokers). Neither of the previous reviews, however, explicitly reported mortality risk estimates for specific exclusions only (e.g. non-smokers only) or combined exclusions (Janssen, and Mark, 2007 & Winter, 2014). Recently, Aune *et al*., (2016) reported an increased mortality risk of 4% (CI 1.01, 1.07) per 5-unit increment in BMI for never smokers aged ≥65 years. Conversely, in the non-linear dose response analysis there was no significant association with mortality for BMI values within the range 24.0 to <45.0 kg/m^2. In the overall analysis (i.e. in all ages) the nadir of the BMI mortality curve was reported to be reduced following exclusions of smokers and those with conditions

associated with weight loss. Combined exclusions for the age group ≥65 years were not reported in the meta-analysis by Aune *et al*., (2016) (Aune *et al.*, 2016).

The Global BMI Mortality Collaboration (2016) individual participant meta-analysis, which was not available at the start of my PhD, reported that the BMI-Obese 1 range was associated with an increased mortality risk (HR 1.19 CI 1.14, 1.23) for never smoking adults aged 70 to 89 years without pre-existing disease, excluding the first five years of follow-up (Di Angelantonio *et al.*, 2016). There was no significant mortality risk for the BMI Overweight range (HR 1.00 CI 0.98, 1.02). Findings from the meta-analysis presented in this chapter are partly in line with those from the Global BMI Mortality Collaboration (2016). However, the mortality association magnitudes for the BMI Overweight and BMI Obese-1 ranges reported in the Global BMI Mortality Collaboration (2016) and the analysis presented in this chapter differ. This may be due to the chosen age range (70 to 89 years in the Global collaboration versus ≥65 years in this chapter). Additionally, it was noted that individual records on chronic conditions were not always complete and thereby residual confounding may have persisted (Di Angelantonio *et al.*, 2016). Questions remain on the BMI associations with mortality using recent measures for narrower age groups.

3.5.2. Analyses included in this review

Comparisons between BMI and mortality analyses can be difficult due to the chosen age groups, model adjustments, baseline period, length of follow-up, and number of years of follow-up excluded. For instance, some studies have used relatively narrow age ranges of within ten years (Adams *et al.*, 2006; Ford, Spallek and Dobson, 2008; de Hollander *et al.*, 2012 b) whereas others have used broader age ranges of ≥30 years (Ma *et al.*, 2013; Koster *et al.*, 2015). Reported mortality risk estimates may be diluted by the inclusion of both the young-old and the oldest-old. The model adjustments for the analyses included in this review were not consistent, and none of these were chosen based on using a directed acyclic graph approach. Most studies had baseline periods within the 1980s and 1990s. Since the 1980s the number of adults with a BMI within the Overweight or Obese range has risen substantially. Additionally, the diagnosis and treatment of many of the cardiovascular risk factors associated with obesity has been

enhanced and therefore mortality risk estimates may be altered (**see Chapter 1**). Most studies had a long follow-up period (≥10 years). Studies which had shorter follow-up periods showed reduced mortality risks for the BMI Overweight range and reduced or non-significant mortality risks for the BMI Obese-1 range relative to the BMI Normal range. This further highlights that shorter follow-up periods are more likely to report reduced/non-significant mortality risks. Deaths during the first few years are likely to reflect undiagnosed disease and thus reverse causation **(see Chapter 1).** Additionally, it can take years for obesity-related conditions to develop. The chosen number of years to exclude during the follow-up for early deaths differed amongst the studies with the shortest amount of time excluded being one month (Graf *et al.*, 2015) and the longest being five years (Dey *et al.*, 2001; Ma *et al.*, 2013; Cheng *et al.*, 2016). Opinions on the need to exclude early mortality have been divided. Empirical data is, therefore, required to assess how many years of follow-up are needed to be excluded to provide stable BMI mortality estimates.

The exclusion criteria, BMI groups, and BMI referent group have also not been consistent between studies. There was no uniformity in the number and choice of conditions to exclude. Previous analyses which excluded persons with conditions associated with weight loss did not empirically test these associations; I will demonstrate this in **Chapter 4**. Only two studies excluded persons with reported weight loss, one excluding those with a loss of ≥10 pounds within the preceding year (Patel, Hildebrand and Gapstur, 2014) and the other a loss of ≥10 pounds within the preceding five years (Baik *et al.*, 2000). The BMI groups representing the BMI Overweight range were not consistent between the studies, with some studies subdividing this range. Although most studies showed similar mortality risks for these subdivisions, there were some instances in which non-significant and increased mortality risks were reported for the lower and higher ends of the BMI Overweight range respectively (Berrington de Gonzalez *et al.*, 2010; Park *et al.*, 2012; Patel, Hildebrand and Gapstur, 2014).

The BMI referent group was not uniform with 18 studies using the standard Normal BMI range and 14 studies using a referent group commencing at a BMI of ≥20 kg/m^2. The two studies which used all three exclusions had a BMI reference range ≥22.0 kg/m^2 (Berrington de Gonzalez *et al.*, 2010; Park *et al.*,

2012). As discussed in **Chapter 1,** another explanation for paradoxical BMI associations (reduced or non-significant mortality risks) is that persons within the lower end of the conventional BMI Normal range may be at an increased mortality risk, thereby distorting mortality risk estimates for the higher BMI ranges. The choice of the BMI referent group will be analysed and discussed further in **Chapter 5.**

Findings from the meta-analysis presented in this chapter highlight that there is a lack of analyses for BMI mortality estimates across the age-range for older adults. None of the analyses included in this review concurrently provided mortality risk estimates for narrower age groups which could be used in this review (some studies did not provide confidence intervals or had less <1000 subjects in additional age groups). There has been a limited number of studies (*n* = 4) which have provided recent BMI mortality estimates e.g. using a baseline period from the 21st Century (Hirani *et al.*, 2014; Holme and Tonstad, 2015; Koster *et al.*, 2015; Cheng *et al.*, 2016). As highlighted in C**hapter 1** the global prevalence of persons classified as obese has risen substantially and there is a need to update the reported associations between higher BMI values and health outcomes. Similarly, there has been an increase in the treatment of many of the metabolic risk factors associated with obesity (hypertension and cholesterol) and, therefore, the estimates for mortality may differ. Analyses of the BMI associations using NHANES I, II, and III has shown a secular decline in mortality from obesity (Flegal *et al.*, 2005).

3.5.3. Strengths and limitations

In this chapter I summarised cohort studies that have reported on the association between the BMI Overweight range and BMI Obese-1 range with all-cause mortality for adults aged ≥65 years. This is the first meta-analysis that has presented mortality risk estimates for both specific exclusions and combined exclusions as well as assessing the contribution of the length of the follow-up period and the choice of the BMI referent group.

There are several limitations with my analysis. One limitation of this review was that the outcome addressed was all-cause mortality. Therefore, risk estimates for the BMI Overweight and BMI Obese-1 ranges with specific causes of death or

morbidity may differ to those presented in this chapter for all-cause mortality. Furthermore, this review focused on adults aged ≥65 years and mortality risk estimates may have been diluted due to the inclusion of younger and older adults. The findings may not be generalisable to populations which were not included in this analysis. Most of the current studies were conducted in the United States of America or Europe (Finland, France, Iceland, Norway, Sweden, Switzerland, the United Kingdom and the SENECA study). A further limitation of this review was that I did not assess the quality of the included studies, for instance by using the Newcastle-Ottawa scale, which may have affected the summary mortality risks. Aune, *et al.*, (2016) highlighted in their meta-analysis that study quality could alter the shape of the BMI mortality curve and the BMI range associated with the lowest mortality risk. For all age-groups, the BMI range associated with lowest mortality risk was higher when summarising studies considered as medium quality compared to studies considered to be high quality (Aune *et al.*, 2016). Additionally, the quality of the data used for summarising the mortality risks could have been enhanced by using individual patients'/participants' data rather than the study data. Conducting a meta-analysis of individual participant data has several advantages including the harmonisation of the inclusion/exclusion criteria, the choice of the statistical model, and covariates (Riley, Lambert and Abo-Zaid, 2010). As highlighted in this chapter, the inclusion/exclusion criteria and the model adjustments were not uniform**.** A final way to enhance this analysis would be to include multiple reviewers searching, extracting, and checking the data.

3.5.4. Future Work

My review and meta-analysis highlighted that there is a lack of analyses which have concurrently reported on the association between the BMI Overweight and BMI Obese-1 ranges and mortality across progressively older age groups. A limited number of studies (*n* = 2) have reported mortality estimates combining all three exclusions (Berrington de Gonzalez *et al.*, 2010; Park *et al.*, 2012) and using baseline periods within the 21st century. In **Chapter 4,** I present an analysis using the Clinical Practice Research Datalink (CPRD) to estimate the association between the WHO BMI categories and mortality for narrower age groups using a baseline period of ≥1st January 2000. Mortality risk estimates for the BMI

categories are reported for the unrestricted sample (no exclusions) and for simultaneous exclusions (smokers, conditions associated with weight loss, and early follow-up) for each age group. Furthermore, I systematically identify conditions associated with weight loss and assess the number of years of early follow-up to exclude to minimise reverse causality and thereby achieve stable mortality risk estimates.

3.6. Conclusions

This meta-analysis showed that the risks for mortality for the BMI Overweight range and BMI Obese-1 range were markedly altered with combined exclusions. For healthier non-smokers (exclusion of conditions associated with weight loss) the BMI Overweight range and BMI Obese-1 range were associated with an elevated risk for mortality relative to those within the BMI Normal range. Outstanding questions remain, however, on the BMI associations with mortality using recent measures from the 21st century across progressively older age groups.

Supplementary material for Chapter 3

List of Figures for Supplementary material for Chapter 3

List of Tables for Supplementary material for Chapter 3

Figure S3.1 | Flow diagram of the study selection

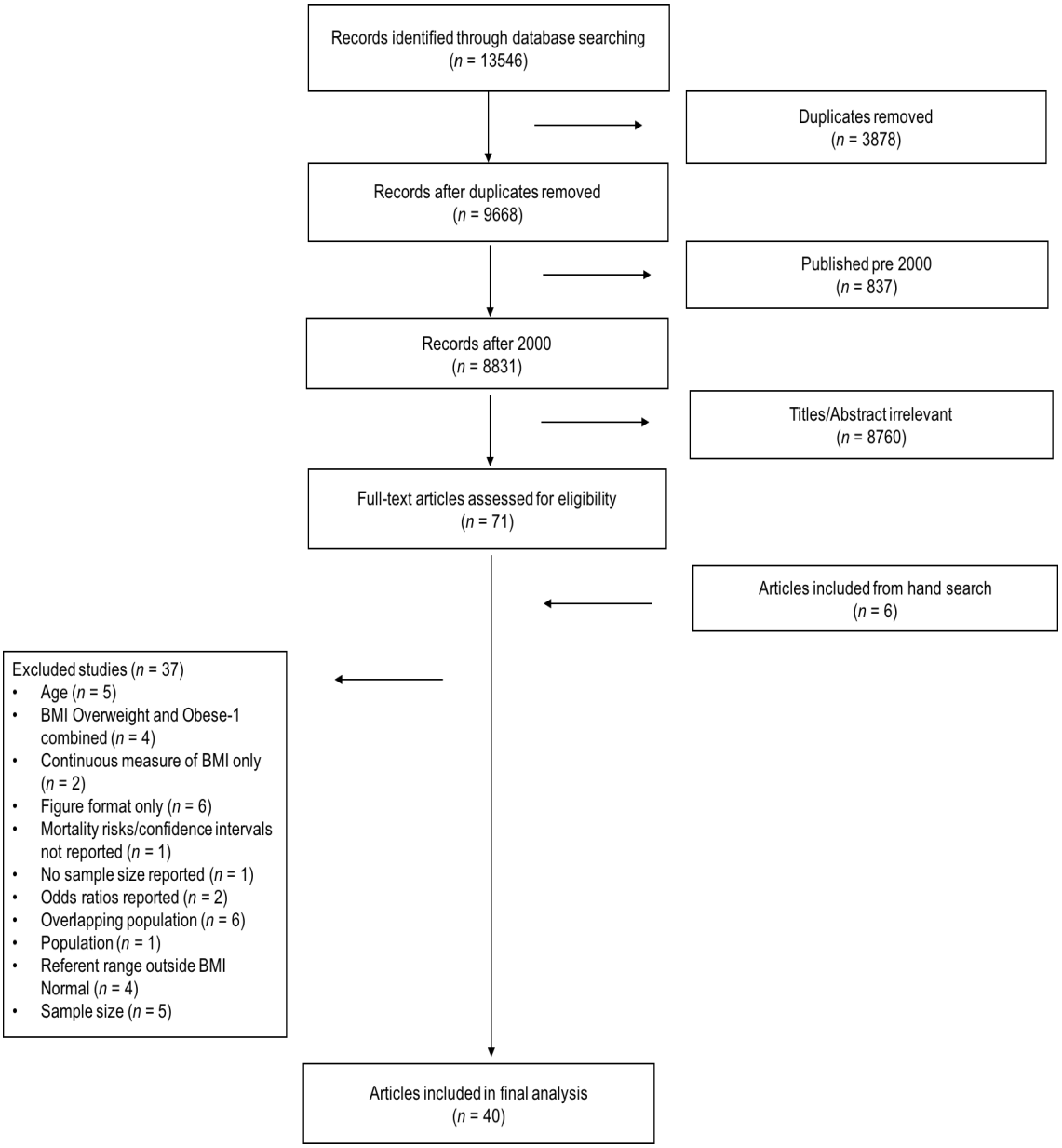


Table S3.1 | Studies or sub-samples excluded from analysis

Author, Year	Study or sample	Reason
(Afzal *et al.*, 2016)	Study: Copenhagen City Heart Study & Copenhagen General Population Study	Age issues
(Ajani *et al.*, 2004)	Study: Physicians' Health Study	Figure format
(Auyeung *et al.*, 2010)	Study: Health check carried out in the School of Public Health of The Chinese University of Hong Kong	Population
(Beleigoli *et al.*, 2013)	Study: Bambuí (Brazil) Cohort Study of Aging	BMI Overweight and obese combined
(Breeze *et al.*, 2006)	Study: Whitehall cohort of male civil servants	BMI overweight and obese combined
(Buys *et al.*, 2014)	Study: University of Alabama at Birmingham Study of Aging	Sample size
(Corrada *et al.*, 2006)	Sample: 70-74 years and 75-79 years	Mortality risk estimates not reported
(Dey *et al.*, 2001a)	Samples: Women excluding Cancer ≤ 70 y & BMI > 40. Restricted to never smokers or quit smoking before 40 y. Plus exclusion of first 5 years	Referent group outside BMI normal range
(Dobson *et al.*, 2012)	Studies: HIMS & ALSWH 1996-1999;1999	Odds ratios reported
(Dutta *et al.*, 2011)	Study: Iowa Established Populations for Epidemiologic Study of the Elderly	Odds ratios reported
(Flegal *et al.*, 2005)	Studies: NHANES I-III 1971-1975; 1976-1980; 1988-1994	Overlapping and no sample size numbers
(Flicker *et al.*, 2010)	Studies: HIMS & ALSWH 1996	Overlapping population

Table S3.1 continued

Author, Year	**Study or sample**	**Reason**
(Grabowski and Ellis, 2001)	Study: Longitudinal Study of Aging (LSOA)	Figure format
(Greenberg, 2001)	Study: National Health and Examination Survey (NHANES 1) Epidemiologic Follow-up Study	Figure format
(Gulsvik *et al.*, 2009)	Study: Bergen Clinical Blood Pressure Study	Sample size
(Klenk *et al.*, 2009)	Study: Vorarlberg Health Monitoring & Promotion Program (VHM&PP)	Figure format
(Koster *et al.*, 2015)	Sample Males aged 66-96 years	Mortality risk estimates not reported
(Kuk and Ardern, 2009)	Study: NHANES III	Sample size
(Kvamme *et al.*, 2012)	Study: Tromsø Study & North-Trøndelag Health Study; 1994-1995; 1996-1997	Referent range outside of BMI Normal
(Lahmann *et al.*, 2002)	Study: Malmo Diet and Cancer Study	Age
(Lang *et al.*, 2008)	Study: ELSA	Mortality risk estimates in figure format
(Lu *et al.*, 2015)	Study: RCAV study	Reference was those aged <40 y & BMI <20
(Masters, Powers and Link, 2013)	Study: 19 waves of NHIS (US)	No sample size numbers and overlapping population
(Mazza *et al.*, 2006)	Study: CASTEL	Reference group outside of BMI Normal range
(Orpana *et al.*, 2009)	Study: National Population Health Survey, a longitudinal panel study conducted by Statistics Canada	Age issues

Table S3.1 continued

Author, Year	**Study or sample**	**Reason**
(Pischon *et al.*, 2008)	Study: EPIC	Sample size / mortality numbers not reported for oldest age group
(Reis *et al.*, 2009)	Study: NHANES	Overlapping population
(Rillamas-Sun *et al.*, 2014)	Study: WHI OS & CT programs	Odds ratios and overlapping population
(Rogers, Hummer and Krueger, 2003)	Study: NHIS	No confidence interval
(Rolland *et al.*, 2014)	Study: EPIDOS study	Continuous measure
(Schneider *et al.*, 2010)	Study: DETECT and SHIP	Figure format
(Schonberg *et al.*, 2011)	Study: National Health Interview Survey (NHIS, 2001–2004)	BMI Overweight and obese combined
(Sergi *et al.*, 2005)	Study: The Italian Longitudinal Study on Aging	BMI referent outside of the Normal range
(Singh *et al.*, 2011)	Study: Adventist Health Study and Adventist Mortality Study in California.	BMI overweight and obese combined
(Stessman *et al.*, 2009)	Study: West Jerusalem residents	Sample size
(Suemoto *et al.*, 2015)	Study: SABE Study	Age issues
(Thomson *et al.*, 2016)	Study: WHI	Figure format and overlapping population
(Van Uffelen *et al.*, 2010)	Study: ALSWH	Continuous measure
(Walter *et al.*, 2009)	Study: Rotterdam Study cohort,	Age issues
(Zunzunegui *et al.*, 2012)	Study: The Aging in Leganés cohort	Sample size

Table S3.2 | Combining of reported risk estimates using fixed effect models for unrestricted analyses (no exclusion of smokers, conditions associated with weight loss or early follow up)

Author, Year	**Gender or age group**	**BMI group**	**Reported Estimate HR (95% CI)**	**Combined HR (95% CI)**
Adams, 2006 (Adams *et al.*, 2006)	Males	25.0-26.4	0.91 (0.87, 0.96)	
	Males	26.5-27.9	0.95 (0.90, 1.00)	
	Males	28.0-29.9	0.96 (0.91, 1.01)	
	Males	*25.0-29.9*	-	*0.94 (0.91, 0.97)*
	Females	25.0-26.4	1.01 (0.92, 1.10)	
	Females	26.5-27.9	1.04 (0.95, 1.14)	
	Females	28.0-29.9	1.06 (0.97, 1.16)	
	Females	*25.0-29.9*	-	*1.04 (0.98, 1.09)*
	Males & Females	*25.0-29.9*	-	*0.97 (0.94, 0.99)*
	Males	30.0-34.9	1.05 (0.99, 1.10)	
	Females	30.0-34.9	1.14 (1.05, 1.23)	
	Males & Females	*30.0-34.9*	-	*1.08 (1.03, 1.13)*
Holme, 2015 (Holme and Tonstad, 2015)	Males	25.0-27.4	0.91 (0.78, 1.00)	
	Males	27.5-29.9	0.86 (0.76, 0.98)	
	Males	25.0-29.9	-	*0.89 (0.81, 0.97)*

Table S3.3 | Combining of reported risk estimates using fixed effect models for restricted analyses

Author, Year	Gender or age group	BMI group	Reported Estimate HR (95% CI)	Combined HR (95% CI)
Baik, 2000 (Baik *et al.*, 2000)	Males	25.0-26.9	0.75 (0.53, 1.08)	
	Males	27.0-29.9	0.83 (0.56, 1.23)	
	Males	25.0-29.9	-	0.79 (0.60, 1.02)
Berrington de Gonzalez, 2010 (Berrington de Gonzalez *et al.*, 2010)	Males & Females	25.0-27.4	1.04 (0.96, 1.13)	
	Males & Females	27.5-29.9	1.15 (1.04, 1.26)	
	Males & Females	25.0-29.9	-	1.08 (1.02, 1.15)
Dey, 2001 (Dey *et al.*, 2001)	Males	26.5-28.5	1.01(0.81, 1.26)	
	Females	26.6-29.2	1.16 (0.88, 1.52)	
	Males & Females	Overweight range	-	1.07 (0.9, 1.27)
Ellekjaer, 2001 (Ellekjaer, Holmen and Vatten, 2001)	Males	25.11-27.35	0.80 (0.69, 0.93)	
	Females	25.98-29.00	0.62 (0.52, 0.75)	
	Males & Females	Overweight range	-	0.72 (0.64, 0.81)
	Males	25.0-29.9	0.77 (0.57, 1.03)	
	Females	25.0-29.9	1.09 (0.89, 1.33)	
	Males & Females	25.0-29.9		0.98 (0.83, 1.15)
	Males	30.0-34.9	1.15 (0.70, 1.89)	
	Females	30.0-34.9	1.44 (1.08, 1.92)	
	Males & Females	30.0-34.9		1.36 (1.06, 1.75)
Graf, 2015 (Graf *et al.*, 2015)	Males	25.0-29.9	0.76 (0.66, 0.88)	
	Females	25.0-29.9	0.89 (0.74, 1.07)	
	Males & Females	25.0-29.9	-	0.81 (0.72, 0.90)

Table S3.3 continued

Author, Year	**Gender or age group**	**BMI group**	**Reported Estimate HR (95% CI)**	**Combined HR (95% CI)**
Graf, 2015 (Graf *et al.*, 2015)	Males	30.0-34.9	0.53 (0.40, 0.70)	
	Females	30.0-34.9	1.02 (0.80, 1.30)	
	Males & Females	30.0-34.9	-	0.77 (0.64, 0.92)
Moore, 2008 (Moore *et al.*, 2008)	Females	25.0-27.4	1.17 (1.02, 1.34)	
	Females	27.5-29.9	1.01 (0.84, 1.21)	
	Females	25.0-29.9	NA	1.11 (1.00, 1.24)
Park, 2012 (Park *et al.*, 2012)	Males	25.0-27.4	1.03 (0.89, 1.18)	
	Males	27.5-29.9	1.23 (1.04, 1.46)	
	Males	25.0-29.9	-	1.11 (0.99, 1.23)
	Females	25.0-27.4	1.03 (0.92, 1.17)	
	Females	27.5-29.9	1.11 (0.97, 1.27)	
	Females	25.0-29.9	-	1.06 (0.97, 1.16)
	Males & Females	25.0-29.9	-	1.08 (1.01, 1.16)
	Males	30.0-34.9	1.46 (1.21, 1.75)	
	Females	30.0-34.9	1.36 (1.19, 1.55)	
	Males & Females	30.0-34.9	-	1.39 (1.25, 1.55)

Table S3.3 continued

Author, Year	Gender or age group	BMI group	Reported Estimate HR (95% CI)	Combined HR (95% CI)
Patel, 2014 (Patel, Hildebrand and Gapstur, 2014)	Males	25.0-27.4	1.00 (0.94, 1.05)	
	Males	27.5-29.9	1.08 (1.01, 1.16)	
	Males	25.0-29.9	-	1.03 (0.99, 1.08)
	Females	25.0-27.4	1.02 (0.99, 1.06)	
	Females	27.5-29.9	1.07 (1.02, 1.12)	
	Females	25.0-29.9	-	1.04 (1.01, 1.07)
	Males & Females	25.0-29.9	-	1.04 (1.01, 1.06)
	Males	30.0-34.9	1.06 (0.95, 1.17)	
	Females	30.0-34.9	1.13 (1.08, 1.19)	
	Males & Females	30.0-34.9	-	1.12 (1.07, 1.17)
Price, 2006 (Price *et al.*, 2006)	Males	>25.0-26.7	0.77 (0.67, 0.88)	
	Males	>26.7-29.0	0.73 (0.63, 0.85)	
	Males	25.0-29.0	-	0.75 (0.68, 0.83)
	Females	26.8-29.7	0.76 (0.67, 0.87)	
	Males & Females	Overweight range	-	0.75 (0.70, 0.82)
Reuser, 2008 (Reuser, Bonneux and Willekens, 2008)	Males	25.0-29.9	0.86 (0.70, 1.06)	
	Females	25.0-29.9	0.80 (0.66, 0.98)	
	Males & Females	25.0-29.9		0.83 (0.72, 0.96)
	Males	30.0-34.9	0.85 (0.60, 1.21)	
	Females	30.0-34.9	0.95 (0.72, 1.26)	
	Males & Females	30.0-34.9		0.91 (0.73, 1.13)

Table S3.3 continued

Author, Year	Gender or age group	BMI group	Reported Estimate HR (95% CI)	Combined HR (95% CI)
Wee, 2011 (Wee, 2011)	Males	25.0-27.4	0.84 (0.78, 0.92)	
	Males	27.5-29.9	0.81 (0.73, 0.90)	
	Males	25.0-29.9	-	0.83 (0.78, 0.88)
	Females	25.0-27.4	0.90 (0.81, 0.99)	
	Females	27.5-29.9	0.82 (0.74, 0.92**)**	
	Females	25.0-29.9	-	0.86 (0.80, 0.93)
	Males & Females	25.0-29.9	-	0.84 (0.80, 0.88)
	Males	30.0-34.9	0.89 (0.81, 0.99)	
	Females	30.0-34.9	0.98 (0.88, 1.08)	
	Males & Females	30.0-34.9	-	0.93 (0.87, 1.00)
Xiao, 2014 (Xiao *et al.*, 2014)	Males	25.0-29.9	1.06 (0.98, 1.16)	
	Females	25.0-29.9	1.03 (0.93, 1.15)	
	Males & Females	25.0-29.9	-	1.05 (0.98, 1.12)
	Males	30.0-34.9	1.31 (1.17, 1.46)	
	Females	30.0-34.9	1.26 (1.10, 1.43)	
	Males & Females	30.0-34.9	-	1.29 (1.18, 1.40)

Table S3.4 | Exclusions of studies which had adjusted for intermediates along the causal pathway

Analyses	**Author(s) of study/studies excluded**	**Summary estimates**	I^2
Overweight and exclusion of conditions associated with weight loss	Cheng, 2016 (Cheng *et al.*, 2016) Ellekjaer, 2001 (Ellekjaer, Holmen and Vatten, 2001) Yates, 2008 (Yates, Djousse and Kurth, 2013)	1 study in analysis after excluding Cheng, Ellekjaer, and Yates.	
Overweight and exclusion of smokers only	Cheng, 2016 (Cheng *et al.*, 2016)	0.91 (0.82, 1.01)	42.5
Overweight exclusion smokers and deaths all follow up & ≥ 10y follow up	Cheng, 2016 (Cheng *et al.*, 2016)	1 study left in the analysis	
Overweight and exclusion of smokers only & ≥ 10y follow up	Cheng, 2016 (Cheng *et al.*, 2016)	0.97 (0.92, 1.01)	0.0
Overweight and exclusion of smokers only & standard BMI Normal as the reference	Cheng, 2016 (Cheng *et al.*, 2016)	0.91 (0.82, 1.01)	42.5
Overweight and exclusion of smokers only and deaths & standard BMI Normal as the reference	Cheng, 2016 (Cheng *et al.*, 2016)	1 study left in the analysis	
Overweight and exclusion of smokers only & standard BMI Normal as the reference& ≥ 10y follow up	Cheng, 2016 (Cheng *et al.*, 2016)	0.91 (0.82, 1.01)	42.5

Table S3.4 continued

Analyses	**Author(s) of study/studies excluded**	**Summary estimates**	I^2
Overweight and exclusion of smokers only and deaths & standard BMI Normal as the reference & ≥ 10y follow up	Cheng, 2016 (Cheng *et al.*, 2016)	1 study left in the analysis	
Obese-1 and exclusion of smokers only	Cheng, 2016 (Cheng *et al.*, 2016)	1 study left in the analysis	
Obese-1 exclusion smokers and deaths	Cheng, 2016 (Cheng *et al.*, 2016)	1 study left in the analysis	
Obese-1 and exclusion of smokers only & ≥ 10y follow up	Cheng, 2016 (Cheng *et al.*, 2016)	1 study left in the analysis	
Obese-1 exclusion smokers and deaths & ≥ 10y follow up	Cheng, 2016 (Cheng *et al.*, 2016)	1 study left in the analysis	
Obese-1 and exclusion of smokers only & BMI Normal as the reference	Cheng, 2016 (Cheng *et al.*, 2016)	1 study left in the analysis	
Obese-1 exclusion smokers and deaths & BMI Normal as the reference	Cheng, 2016 (Cheng *et al.*, 2016)	1 study left in the analysis	
Obese-1 and exclusion of smokers only & BMI Normal as the reference & ≥ 10y follow up	Cheng, 2016 (Cheng *et al.*, 2016)	1 study left in the analysis	

Table S3.4 continued

Analyses	**Author(s) of study/studies excluded**	**Summary estimates**	I^2
Obese-1 exclusion smokers and deaths & BMI Normal as the reference & ≥ 10y follow up	Cheng, 2016 (Cheng *et al.*, 2016)	1 study left in the analysis	
Unrestricted Overweight	Holme, 2015 (Holme and Tonstad, 2015)	0.88 (CI 0.84, 0.91)	63.8
Unrestricted Overweight & ≥ 10y follow up	Holme, 2015 (Holme and Tonstad, 2015)	0.91 (CI 0.86, 0.95)	57.7
Unrestricted Overweight & with BMI referent ≥20	Holme, 2015 (Holme and Tonstad, 2015)	0.91 (CI 0.85, 0.98)	62.4
Unrestricted Overweight & with BMI referent ≥20 & ≥ 10y follow up	Holme, 2015 (Holme and Tonstad, 2015)	0.97 (0.95, 0.99)	0.0
Unrestricted Obese-1	Holme, 2015 (Holme and Tonstad, 2015)	0.92 (CI 0.82,1.02)	82.4
Unrestricted Obese-1 & ≥ 10y follow up	Holme, 2015 (Holme and Tonstad, 2015)	0.98 (CI 0.87, 1.11)	73.7
Unrestricted Obese-1 & with BMI referent ≥20	Holme, 2015 (Holme and Tonstad, 2015)	0.92 (0.67, 1.27)	94.3
Unrestricted Obese-1 & with BMI referent ≥20 & ≥ 10y follow up	Holme, 2015 (Holme and Tonstad, 2015)	1 study in analysis after excluding Holme, 2015	

Chapter 4 Associations between the WHO BMI categories and mortality for progressively older age groups using electronic health records (Clinical Practice Research Datalink)

Table of Contents

List of Tables for Chapter 4

List of Figures for Chapter 4

4.1. Overview of the chapter

This chapter is based mainly on my first author published paper:

> Bowman, K., Delgado, J., Henley, W.E., Masoli, J.A., Kos, K., Brayne, C., Thokala, P., Lafortune, L., Kuchel, G.A., Ble, A., & Melzer, D. (2017) Obesity in Older People With and Without Conditions Associated With Weight Loss : Follow-up of 955,000 Primary Care Patients. J Gerontol A Biol Sci Med Sci. Editor's Choice. 72(2): 203–209.

My contribution to this published work included conducting the literature review, designing and conducting the analyses, and writing the manuscript. Therefore, much of the **methods, results** and **discussion** are **direct translations** from this paper. Some sentences have been modified to make the sentences clearer and additional headings have been used.

I have, however, **redrafted** the **abstract, introductory** section, and **concluding remarks** to emphasise the links throughout this thesis. Additionally, I have restructured parts of the original manuscript with some of the supplementary material now added to this chapter to make clearer the progression of the analysis. I have also changed some of the formatting of the supplementary material e.g. tables in the original manuscript have been changed to forest plots and are now within the main text. I have also added an additional analysis to this chapter where the mortality model was additionally adjusted for physical activity. Furthermore, additional sections have been added to the discussion to show the links throughout this thesis.

4.2. Summary

Background: Older people within the body mass index (BMI) defined Obese-1(30.0-34.9 kg/m^2) range reportedly have lower or similar mortality risks to those within the conventional BMI Normal range (18.5-24.9 kg/m^2), termed the obesity paradox, casting doubt on responses to the obesity epidemic. However, these estimates may be distorted by pooling relatively healthy subjects, smokers, and those with conditions associated with weight loss.

Objective: To estimate BMI associations with mortality across progressively older age groups in a sufficiently large primary care population to allow stratified analyses.

Design: This analysis used the Clinical Practice Research Datalink (CPRD) which contains primary care, hospital, and death certificate electronic health records for registered populations aged ≥60 years in England from 1st January 2000. The analysis included 955,031 patients, with complete data (smoking, alcohol, and socioeconomic status records) available for 822,811 patients. The 'healthier agers' subgroup were non-smokers without conditions associated with weight loss and who survived the first 3.9 years of the follow-up period. Cox proportional hazards models were adjusted for age, gender, alcohol use, smoking, calendar year, and socioeconomic status.

Results: In the 65 to 69 years age group (*n* = 312,352), 13.1% of the subjects died during a maximum follow-up period of 14.9 years. In this age group, those within the BMI Obese-1 range had reduced mortality risks relative to those within the conventional BMI Normal range, with Hazard Ratio (HR) 0.91 (95% Confidence Interval [CI] 0.88, 0.93). However, there was a reversal of the mortality risks for those within the BMI Obese-1 range for 'healthier agers', with an increased mortality risk (HR 1.17 CI 1.11, 1.23). The reversal of the mortality risks with the BMI Obese-1 range was observed up to age 74 years and shifted to non-significance for those aged 75 to 84 years.

Conclusions: The obesity paradox in later life appears to be the erroneous result of combining mortality risks for relatively healthy and already ill older groups. As

obesity is associated with excess mortality in otherwise healthy non-smoking older people, up to and including those aged 74 years, assertions based on the claimed paradox against current obesity control efforts are misplaced.

4.3. Introduction

The worldwide epidemic of obesity clearly requires a concerted, science based response to prevent adverse outcomes. As outlined in **Chapter 1,** younger and middle aged adults within the BMI Obese range are at an increased risk of cancer, cardiovascular disease and premature mortality (Calle *et al.*, 1999; Adams *et al.*, 2006; Renehan *et al.*, 2007; Whitlock *et al.*, 2009; Wormser *et al.*, 2011). In later life (aged ≥65 years) persons within the BMI Obese-1 range have been reported to have reduced or similar mortality risk to those within the conventional BMI Normal range. This opposing mortality risk for the BMI Obese-1 range has been termed the obesity paradox. Flegal *et al.*, (2013) reported that there was a similar mortality risk for adults aged ≥65 years within the BMI Obese-1 (BMI 30.0-34.9 kg/m^2) range relative to those within the conventional BMI Normal (BMI 18.5-24.9 kg/m^2) range. There was a reduced mortality risk for those within the BMI Overweight range (BMI 25.0-29.9 kg/m^2) (Flegal *et al.*, 2013). Dixon and colleagues have argued that this "obesity risk paradox" in older adults is counter to "decades of advice to avoid even modest weight gain", and that current weight control policies may be doing harm in older groups (Dixon *et al.*, 2015). Several previous analyses have documented that the BMI associated with the lowest mortality risk lies within the BMI Overweight range, therefore conferring a protective effect (Flicker *et al.*, 2010; van Uffelen *et al.*, 2010; de Hollander *et al.*, 2012 b; Cheng *et al.*, 2016). There is, therefore, some urgency to clarify whether people with a BMI in the Overweight or Obese-1 range are or are not at greater risk of death.

As discussed in **Chapter 1** BMI is the most widely used adiposity measure in both clinical practice and epidemiological studies. Chang *et al.*, (2014) documented that for males and females aged ≥65 years there was a strong correlation between BMI and body fat percentage measured by dual energy X-ray absorptiometry, r=0.81 and r=0.71, respectively (Chang *et al.*, 2014). The validity and prognostic value of the conventional BMI categories published by the World Health Organization (World Health Organization, 2000) for older adults and ethnic groups has been questioned (Heiat, Vaccarino and Krumholz, 2001; Zamboni *et al.*, 2005; Ntuk *et al.*, 2014; Rolland *et al.*, 2014; Winter *et al.*, 2014).

As highlighted in **Chapter 1** and **Chapter 3** various explanations (Janssen and Mark, 2007; Kalantar-Zadeh *et al.*, 2007; Chiolero *et al.*, 2008) have been offered for the obesity paradox in later life including: biological mechanisms, length of follow-up, reverse causality and smoking. Smoking is associated with lower weight and markedly raised health risks and can therefore distort regression estimates, even when an adjustment is made in models (Chiolero *et al.*, 2008). At older ages, several diseases cause both weight loss and increased mortality, introducing reverse causation confounding into models (Kalantar-Zadeh *et al.*, 2007).

In **Chapter 3**, I showed there were reduced and non-significant mortality risks for the BMI Overweight and BMI Obese-1 ranges in unrestricted analyses (i.e. no exclusion of smokers, early mortality, or weight loss) relative to those within the BMI Normal range. These associations (reduced or non-significant mortality risks) remained in analyses which had only considered one specific exclusion (e.g. smokers). Elevated mortality risks were shown for analyses which excluded smokers, early mortality and conditions associated with weight loss, highlighting the importance of simultaneous exclusions.

However, limitations with the meta-analysis I presented in **Chapter 3** included a lack of studies which had used all three simultaneous exclusions and which reported BMI mortality risks within narrow age bands across the older age range. Inclusion of the youngest old and the oldest old may dilute risk estimates. Furthermore, there was no consistency regarding the number of years to exclude during the follow-up for early deaths, or the number and choice of conditions to exclude.

To clarify obesity risks in later life, well powered recent estimates are needed which account for confounders. Data from the Clinical Practice Research Datalink was analysed as it is representative of the older population. This analysis included English patients registered with primary care and linked to hospital episode statistics (HES). I aimed to estimate the association between the WHO BMI categories and mortality using a large cohort of population representative patients (aged ≥60 years) within narrower age bands, and additionally to estimate the associations in subgroups of ‘healthier agers’ and ‘non-healthier agers’. In

this chapter I sought to address the contributions of the inclusion of smokers, those with conditions associated with weight loss, and the length of follow-up to the obesity paradox.

4.4. Methods

4.4.1. Study Population

Anonymised electronic health records from the CPRD were assessed (Herrett *et al.*, 2015). This analysis included patients with primary care health records linked to Hospital Episode Statistics data and to the Office for National Statistics (ONS) death data. This was available for English patients only. Registration with GPs is nearly complete in the UK and includes patients in institutional settings. The CPRD database includes all patients who are registered with CPRD participating general practices with very few patients withdrawing their data during the study period. CPRD diagnostic and outcome coding has generally high validity, (Herrett *et al.*, 2010) which has been improved further through linkage to hospital and death certificate data.

4.4.2. Patients

All patients with BMI records since the 1st January 2000 and registered with a CPRD practice at the time of measurement were included (BMI records were available for 62% of registered patients, *n* = 955,031), with GP record inclusion to November 17th 2014. Extreme values of BMI were excluded (<14.0 and > 56.5 kg/m^2) (*n* = 6,431). The earliest age at which a BMI was recorded was calculated within the age groups 60 to 64, 65 to 69, 70 to 74, 75 to 84, and 85 years and older. The first BMI record was included for each patient within each age group as the study 'index' BMI for analysis. There were no patient duplications within presented models. For instance, a person could be included in the 60 to 64 age group model and the 70 to 74 age group model if they met all the inclusion criteria. Excluding people from subsequent age group models could result in a disproportionate number of patients who joined practices later or avoided contact with practices in the older age groups. BMI was categorised by the conventional WHO thresholds but the BMI Obese-2 and BMI Obese-3 ranges were combined in those aged ≥85 years as there were <200 patients.

In patients with more than one BMI measure, weight stability was derived (data available for 53.1% patients aged 60 to 64; 58.0% aged 65 to 69; 61.0% aged 70 to 74; 57.4% aged 75 to 84; and 62.7% ≥85 years). Patients were classified as substantial weight losers (lost ≥5 kg), weight gainers (gained ≥5 kg), or weight stable (loss or gain <5 kg), using the weight difference between the study index weight and the mean of all weight records recorded over the preceding 4 years. Smaller fluctuations in weight could reflect measurement errors, acute events, or minor changes due to dieting. The sample was predominantly 'white' ethnicity, e.g. in those aged 65 to 69 years 81.8% had ethnicity data of whom 95.0% were 'white' and 2.3% South Asian.

4.4.3. Lifestyle and socioeconomic variables

Hypothesised causal influences on the BMI association with mortality were formalised in a Directed Acyclic Graph (supplementary material Figure S4.1), which guided covariate selection to avoid inappropriate adjustment for intermediates on the causal pathway. Smoking status was based on GP recorded Read terms in the previous 10 years. Patients were classified as current smokers, ex-smokers, never smokers, and not recorded. Alcohol status was based on GP recorded Read terms and units of alcohol per week (where available) in the previous 10 years (heavy drinkers were defined as >35 units for females and >50 units for males). Patients were classified as heavy drinkers, non-drinkers, current drinkers, former drinkers, and not recorded. Relative socioeconomic status was measured by the Index of Multiple Deprivation 2007 (Mclennan *et al.*, 2010), calculated on each patient's residential postal code and incorporating seven deprivation domains (income, employment, education, health, crime, barriers to housing and services, and living environment) and categorised by quintiles (1 least deprived). Calendar year was included in the models to account for changing trends in BMI recording and medical care during baseline selection. Physical activity was recorded in CPRD as inactive, gentle activity, moderate activity, vigorous activity, or not recorded (most recent data preceding index BMI but up to 10 years before).

4.4.4. Conditions

The following health conditions were coded: asthma, atrial fibrillation, cancer, coronary heart disease, chronic kidney disease stages 3 to 5, chronic obstructive

pulmonary disease, dementia, depression, epilepsy, heart failure, hypertension, hypothyroidism, mental health, stroke and type 2 diabetes. A multi-morbidity or frailty measure was also included which was based on the patient having >6 of 36 Rockwood frailty index conditions (Song, Mitnitski and Rockwood, 2010). The ResearchOne Electronic Frailty Index coding rules were used inclusive of pre-specified symptoms, signs, diseases, disabilities and abnormal laboratory values.

4.4.5. Outcomes

Mortality records were from the Office for National Statistics death certificate data up to the 17th November 2014.

4.4.6. Statistical analysis

Cox proportional hazards models were used to estimate the associations between the WHO BMI categories and mortality. The proportional hazards assumption was tested for each model using Schoenfeld residuals. Multivariate models were adjusted for age, gender, alcohol use, smoking, calendar year, and socioeconomic status. A series of sensitivity analyses were conducted including adjusting for physical activity (where available), excluding those with a previous diagnosis of cardiovascular disease namely angina, myocardial infarction, or stroke, and excluding those with a previous diagnosis of cardiovascular disease or type 2 diabetes. Analyses were carried out using Stata statistical software (version 13.1) and R statistical software (version 3.1.2.).

4.5. Results

4.5.1. Patients with/without BMI measures

Persons with measures of BMI were more likely to suffer from chronic kidney disease, diabetes, or hypertension, and less likely to be diagnosed with heart failure or dementia compared to those without a BMI measure (**Table 4.1**). Furthermore, those with measures of BMI had better survival compared to those without BMI measures, (HR 0.46 95% CI 0.45, 0.46) with adjustment for age, sex and socioeconomic status.

Table 4.1 | Cross sectional analysis of conditions associated with having a BMI record compared to no BMI record for CPRD patients aged ≥60 years using age and sex adjusted logistic regression

Condition	Odds Ratio (95% CI)
Heart Failure	0.64 (0.63, 0.65)
Dementia	0.68 (0.67, 0.69)
Epilepsy	0.80 (0.78, 0.81)
Stroke	0.87 (0.86, 0.88)
Mental Health	0.88 (0.87, 0.90)
Atrial Fibrillation	1.08 (1.07, 1.09)
COPD	1.18 (1.16, 1.19)
CHD	1.19 (1.17, 1.20)
Depression	1.21 (1.20, 1.22)
Recent cancer	1.34 (1.33, 1.36)
Hypothyroidism	1.34 (1.33, 1.36)
Asthma	1.42 (1.40, 1.43)
Hypertension	2.04 (2.02, 2.05)
Type 2 Diabetes	2.39 (2.36, 2.42)
CKD Stages 3 to 5	3.56 (3.51, 3.61)

4.5.2. Empirical identification of conditions

As highlighted in **Chapter 3**, the previous analyses included in the meta-analysis which excluded persons with weight loss associated disease did not empirically test these associations. Excluding chronic conditions that may be associated with weight loss could reduce the generalisability of the results as the prevalence of these conditions increases with advancing age. To identify groups most susceptible to prior weight loss, associations with 15 major diagnoses ascertained before the index BMI measures were tested (**Table 4.2**). In age and gender adjusted regression models against weight loss, cancer (excluding non-melanoma skin cancer) within the preceding five years, dementia, heart failure, and multi-morbidity all yielded Odds Ratios (OR) of ≥1.5 for weight loss, with other conditions having ORs <1.5. These conditions were, therefore, excluded as part of the 'healthier agers' subgroup.

Table 4.2 | Cross sectional analysis of conditions associated with measured weight loss

Condition	Odds Ratio (95% CI)
Dementia	2.00 (1.82, 2.21)
Cancer (within 5 years)	1.61 (1.53, 1.69)
Heart Failure	1.53 (1.44, 1.63)
Mental Health	1.40 (1.29, 1.52)
Atrial Fibrillation	1.39 (1.32, 1.47)
COPD	1.36 (1.30, 1.43)
Epilepsy	1.19 (1.08, 1.32)
Depression	1.16 (1.12, 1.20)
Hypothyroidism	1.15 (1.10, 1.21)
Stroke	1.12 (1.06, 1.18)
Diabetes	1.08 (1.05, 1.12)
CKD Stages 3 to 5	1.08 (1.01, 1.15)
Asthma	1.06 (1.02, 1.10)
Hypertension	1.02 (0.99, 1.05)
CHD	0.89 (0.86, 0.92)

Note: Logistic regression was used for the outcome weight loss adjusted for age and gender for patients aged 65 to 100 years with a first BMI measure since 1st January 2000 who were currently registered and classified as weight losers (≥ 5kg) or stable weight (0 to +/- 4.9 kg). This was calculated as the difference between the study index weight and the mean weights recorded over the preceding 4 years. The logistic regression was run after excluding patients with multi-morbidity.

4.5.3. Baseline characteristics of patients with BMI measures

There were 955,031 patients in the analyses (822,811 with complete data, i.e. no missing values for smoking, alcohol use, or socioeconomic status), with 1,540,553 patient follow-ups with some patients contributing in >1 age-specific analysis. The maximum follow-up duration was 14.9 years (mean 5.97 years, SD 4.02 years). The mean BMI was 28.2 kg/m^2 for those aged 60 to 64 years and 24.8 kg/m^2 for those aged ≥85 years at baseline (**Table 4.3** and supplementary material Table S4.1). Covariate distributions also showed age group trends with, for example, current smoking declining from 34.2% in those aged 60 to 64 years to 19.7% in those aged ≥85 years at baseline. Substantial measured weight loss was present in 5.2% and 11.5% of the youngest and oldest groups, respectively.

4.5.4. Mortality

Overall 13.2% (*n* = 48,442) of those aged 65 to 69 years died during follow-up, with rates rising to 56.9% (*n* = 67,814) in those aged ≥85 years at baseline (supplementary material Table S4.2). While group mean BMI declined modestly with advancing age, it declined markedly for 13 years before death **(Figure 4.1):** for example in those aged 65 to 69 years at baseline, 34% were classified as BMI Obese-1 13 years before death but only 24% in the year of death, while the proportion of those within the BMI Normal range increased from 23% to 39% over the same period.

Table 4.3 | Characteristics of the sample (complete cases with no missing data on smoking status, alcohol status or socioeconomic status) from the CPRD

	Age group (years)				
	60 to 64	**65 to 69**	**70 to 74**	**75 to 84**	**≥85**
n	340,753	312,352	265,912	278,422	96,498
Follow-up years, mean (SD)	5.7 (3.9)	5.5 (3.9)	5.5 (3.8)	5.3 (3.6)	3.6 (2.7)
Age years, mean (SD)	61.8 (1.4)	66.6 (1.4)	71.6 (1.4)	77.7 (2.7)	87.1 (2.6)
Gender					
Females, *n* (%)	173,747 (51.0)	156,075 (50.0)	136,522 (51.3)	153,563 (55.2)	60,713 (62.9)
BMI (kg/m^2), mean (SD)	28.2 (5.4)	28.0 (5.3)	27.6 (5.1)	26.7 (4.9)	24.8 (4.5)
BMI (kg/m^2), n (%)					
Underweight 14.0 to <18.5	3,882 (1.1)	3,917 (1.3)	4,443 (1.7)	7,692 (2.8)	6,260 (6.5)
Normal weight 18.5 to <25.0	93,428 (27.4)	86,315 (27.6)	78,498 (29.5)	100,107 (36.0)	46,396 (48.1)
Overweight 25.0 to <30.0	135,154 (39.7)	126,911 (40.6)	109,126 (41.0)	109,431 (39.3)	31,720 (32.9)
Obese-1 30.0 to < 35.0	72,102 (21.2)	64,981 (20.8)	52,292 (19.7)	45,264 (16.3)	9,823 (10.2)
Obese- 2 35.0 to < 40.0	24,888 (7.3)	21,247 (6.8)	15,827 (6.0)	12,201 (4.4)	1,891 (2.0)
Obese-3 ≥40.0	11,299 (3.3)	8,981 (2.9)	5,726 (2.2)	3,727 (1.3)	408 (0.4)

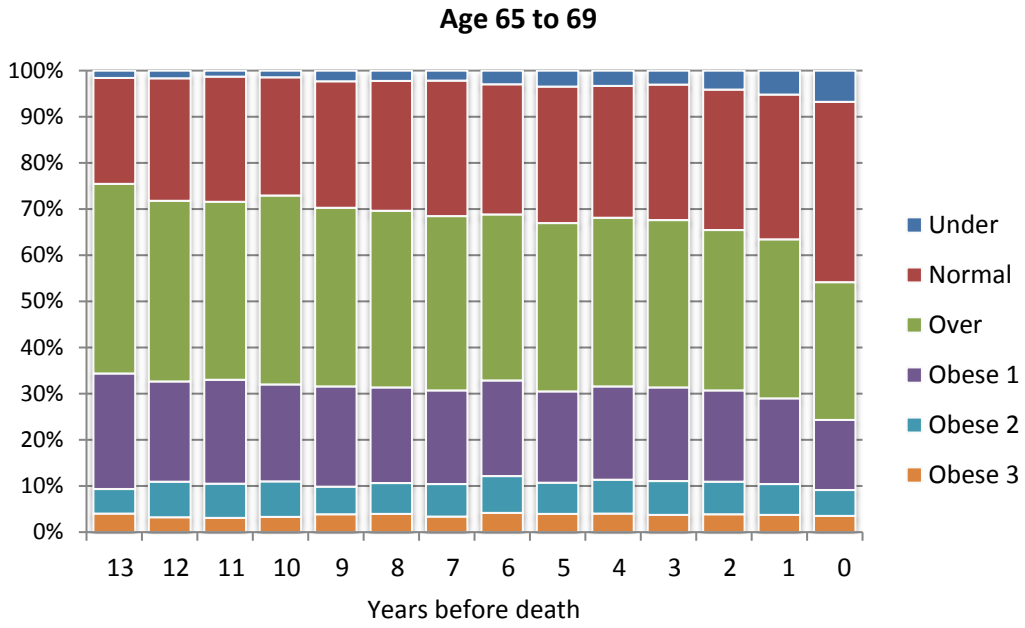
Table 4.3 continued

	60 to 64	65 to 69	70 to 74	75 to 84	≥85
Alcohol Status, n (%)					
Non-drinker	40,021 (11.7)	40,431 (12.9)	39,304 (14.8)	49,391 (17.7)	20,462 (21.2)
Current drinker	220,992 (64.9)	201,070 (64.4)	171,597 (64.5)	180,801 (64.9)	60,220 (62.4)
Ex drinker	11,428 (3.4)	12,223 (3.9)	11,878 (4.5)	13,417 (4.8)	6,520 (6.8)
Heavy drinker	68,312 (20.1)	58,628 (18.8)	43,133 (16.2)	34,813 (12.5)	9,296 (9.6)
Smoking Status, n (%)					
Never	143,886 (42.2)	128,225 (41.1)	110,662 (41.6)	123,469 (44.4)	45,502 (47.2)
Current smoker	116,548 (34.2)	100,612 (32.2)	78,108 (29.4)	68,180 (24.5)	19,026 (19.7)
Ex-smoker	80,319 (23.6)	83,515 (26.7)	77,142 (29.0)	86,773 (31.2)	31,970 (33.1)
Index of multiple deprivation quintiles, n (%)					
1 (least deprived)	77,668 (22.8)	70,691 (22.6)	59,180 (22.3)	60,576 (21.8)	20,543 (21.3)
2	83,863 (24.6)	77,879 (24.9)	66,048 (24.8)	67,994 (24.4)	23,569 (24.4)
3	71,697 (21.0)	65,829 (21.1)	55,992 (21.1)	58,986 (21.2)	21,022 (21.8)
4	64,444 (18.9)	59,202 (19.0)	51,336 (19.3)	55,050 (19.8)	19,148 (19.8)
5	43,081 (12.6)	38,751 (12.4)	33,356 (12.5)	35,816 (12.9)	12,216 (12.7)

Table 4.3 continued

	60 to 64	65 to 69	70 to 74	75 to 84	≥85
Diagnosed disease at baseline, n (%)					
Recent cancer (<5 years)	13,153 (3.9)	16,156 (5.2)	17,418 (6.6)	21,681 (7.8)	8,999 (9.3)
Dementia	685 (0.2)	1,177 (0.4)	2,271 (0.9)	7,190 (2.6)	8,076 (8.4)
Heart Failure	5,699 (1.7)	8,782 (2.8)	11,979 (4.5)	21,139 (7.6)	14,021 (14.5)
Diabetes	39,879 (11.7)	45,137 (14.5)	44,521 (16.7)	45,671 (16.4)	16,558 (17.2)
Coronary Heart Disease	20,457 (6.0)	25,471 (8.2)	27,818 (10.5)	34,572 (12.4)	16,296 (16.9)
Electronic frailty index (score of 6 or more), n (%)	15,072 (4.4)	23,702 (7.6)	32,649 (12.3)	52,477 (18.9)	34,940 (36.2)
Weight stability (4 years prior to BMI record) subgroup, n (%)	180,926 (53.1)	181,302 (58.0)	162,158 (61.0)	159,693 (57.4)	60,463 (62.7)
Weight stable (weight loss or gain of 0 to <5.0 kg) in subgroup	135,740 (75.0)	139,237 (76.8)	128,079 (79.0)	125,986 (78.9)	45,470 (75.2)
Weight loss of ≥5 kg in subgroup	17,699 (9.8)	18,248 (10.1)	16,869 (10.4)	19,345 (12.1)	11,063 (18.3)
Weight gain of ≥5 kg in subgroup	27,487 (15.2)	23,817 (13.1)	17,210 (10.6)	14,362 (9.0)	3,930 (6.5)

Figure 4.1 | Percentage of those aged 65 to 69 years at baseline by conventional BMI category and number of years to death

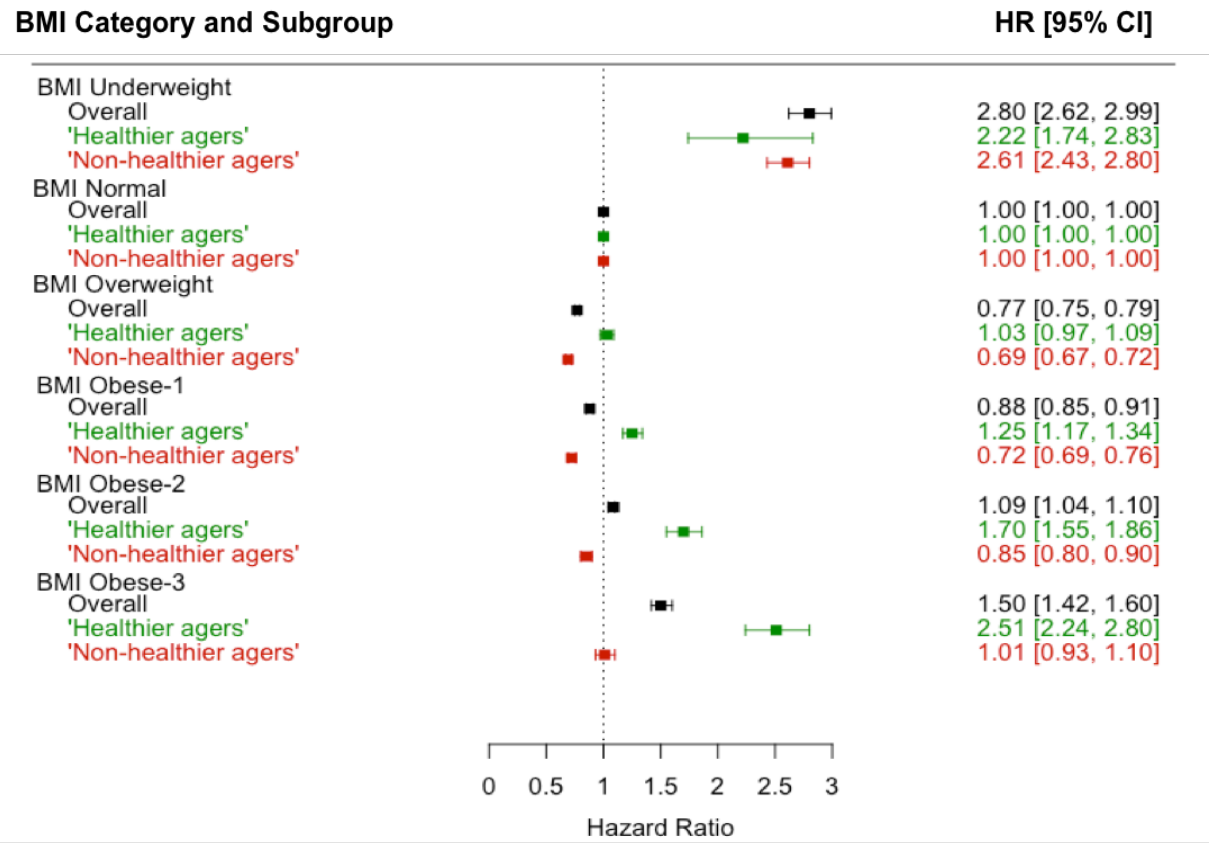


4.5.5. The paradoxical model for mortality hazards

To replicate approaches similar with those producing paradoxical risk estimates (i.e. no exclusions), Cox proportional hazards models for all-cause mortality were computed, adjusting for age, gender, alcohol intake, smoking status, calendar year, and an area-based measure of relative socioeconomic position for all subjects with complete data. All follow-up data from baseline to 14.9 years was included. **Figures 4.2-4.6** present the mortality risks for each age group by the conventional BMI categories for the overall sample (complete cases) in **black** (supplementary material Table S4.3). For those aged 65 to 69 years at baseline (*n* = 312,352 with 40,815 deaths), those within the BMI Obese-1 range had reduced mortality risks relative to those within the conventional BMI Normal range (BMI Obese-1 HR 0.91 95% CI 0.88, 0.93), and estimates were even more paradoxical for the BMI Overweight range (HR 0.79 CI 0.77, 0.81). There were increased mortality risks for those within the BMI Obese-2 range (HR 1.07 CI 1.02, 1.11) and for those within the BMI Obese-3 range (HR 1.54 CI 1.46, 1.63). A similar pattern of paradoxical mortality hazards was present across the other age groups studied for both the BMI Overweight and BMI Obese-1 ranges compared to the conventional BMI Normal range. Incidentally, the highest

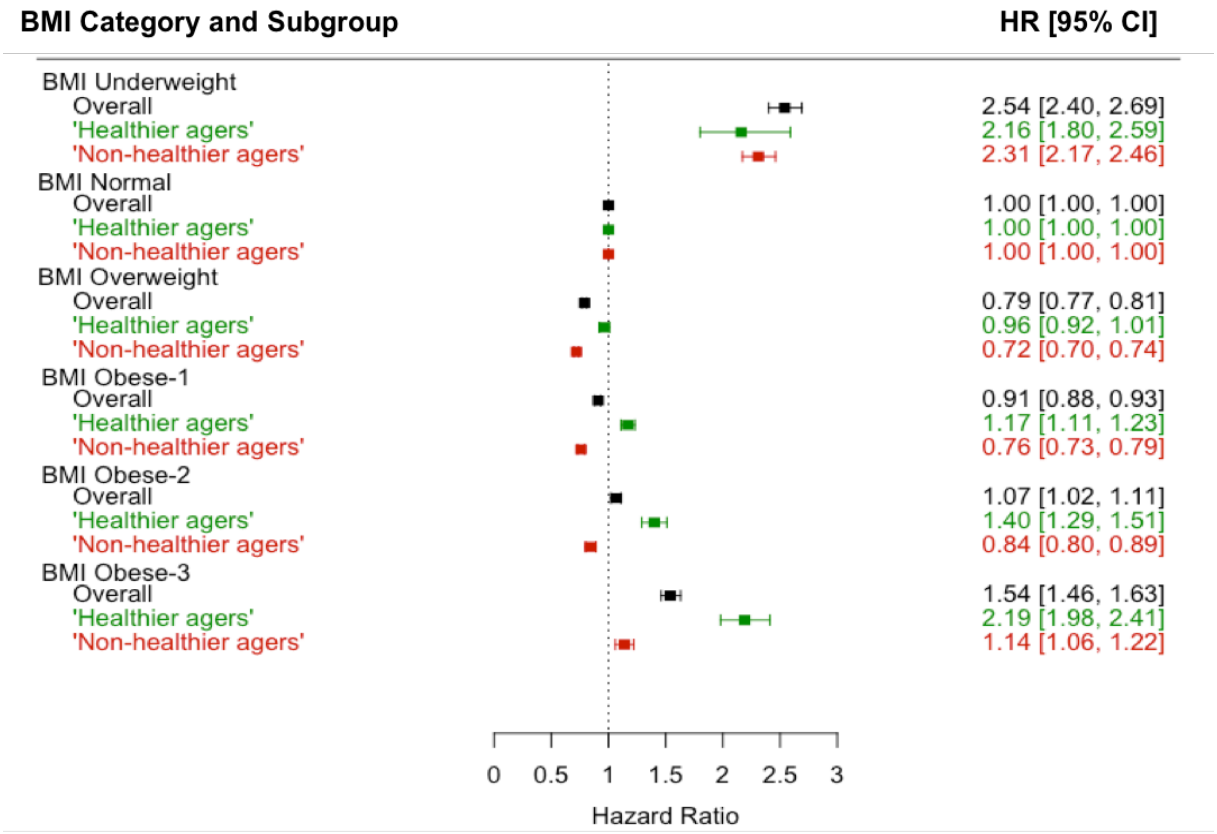
mortality risks were for the BMI Underweight range (age group 65 to 69 years, HR 2.54 CI 2.40, 2.69).

Figure 4.2 | Hazard ratios (95% CI) for all-cause mortality by conventional BMI categories for those aged 60 to 64 years at baseline for the overall sample (**black**), 'healthier agers' (**green**) and 'non-healthier agers' (**red**) from the CPRD. Cox proportional hazards were adjusted for age, gender, alcohol status, smoking status, calendar year, and socioeconomic status



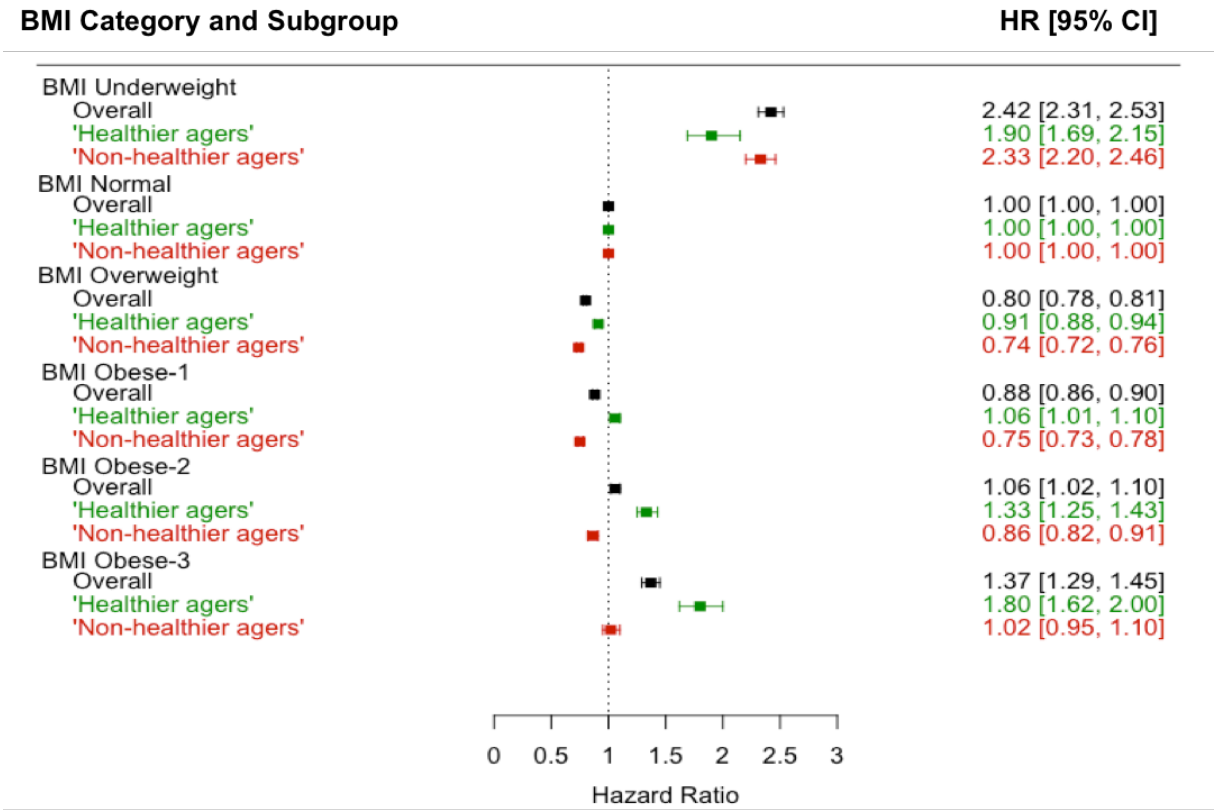
Note: 'Healthier agers' were non-smokers without recent cancer (within the previous five years excluding non-melanoma skin cancer), dementia, heart failure, or multi-morbidity and survived the first 3.9 years. 'Non-healthier' agers were smokers, those with recent cancer (within the previous five years excluding non-melanoma skin cancer), dementia, heart failure, and multi-morbidity.

Figure 4.3 | Hazard ratios (95% CI) for all-cause mortality by conventional BMI categories for those aged 65 to 69 years at baseline for the overall sample (**black**), 'healthier agers' (**green**) and 'non-healthier agers' (**red**) from the CPRD. Cox proportional hazards were adjusted for age, gender, alcohol status, smoking status, calendar year, and socioeconomic status



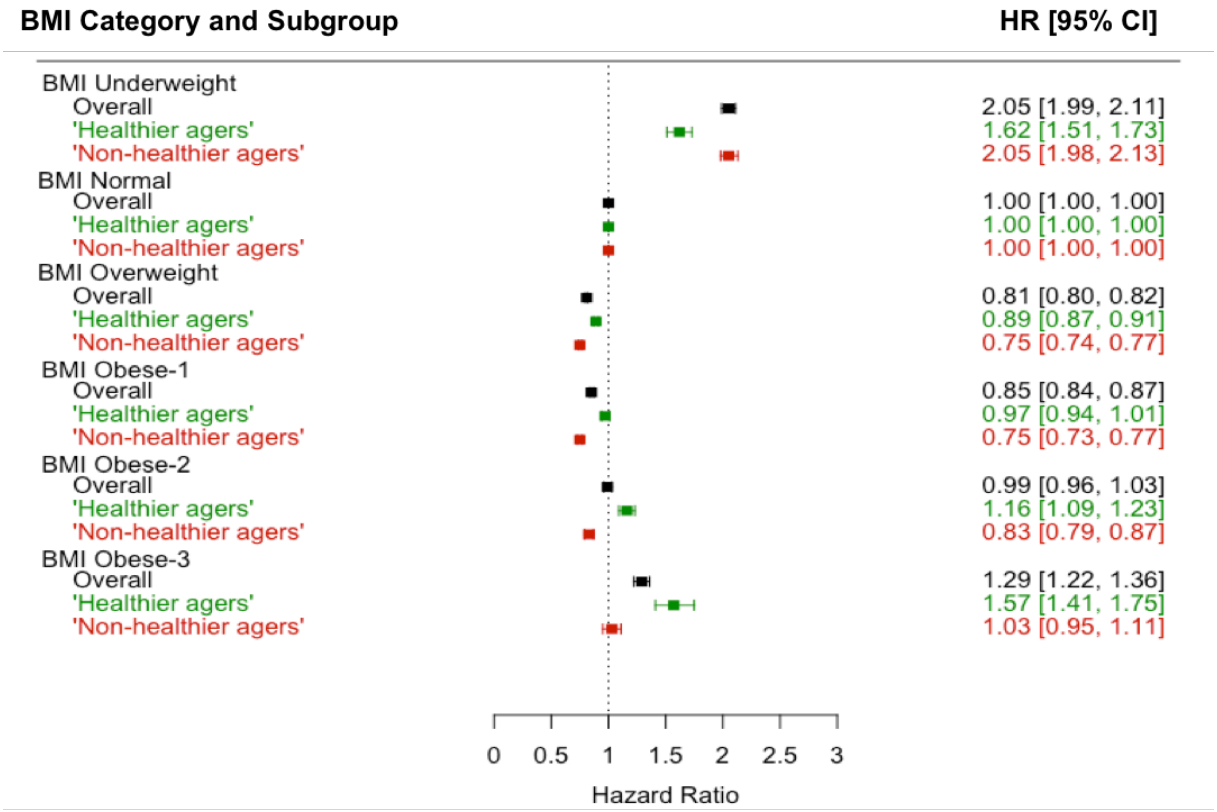
Note: 'Healthier agers' were non-smokers without recent cancer (within the previous five years excluding non-melanoma skin cancer), dementia, heart failure, or multi-morbidity and survived the first 3.9 years. 'Non-healthier' agers were smokers, those with recent cancer (within the previous five years excluding non-melanoma skin cancer), dementia, heart failure, and multi-morbidity.

Figure 4.4 | Hazard ratios (95% CI) for all-cause mortality by conventional BMI categories for those aged 70 to 74 years at baseline for the overall sample (**black**), 'healthier agers' (**green**) and 'non-healthier agers' (**red**) from the CPRD. Cox proportional hazards were adjusted for age, gender, alcohol status, smoking status, calendar year, and socioeconomic status



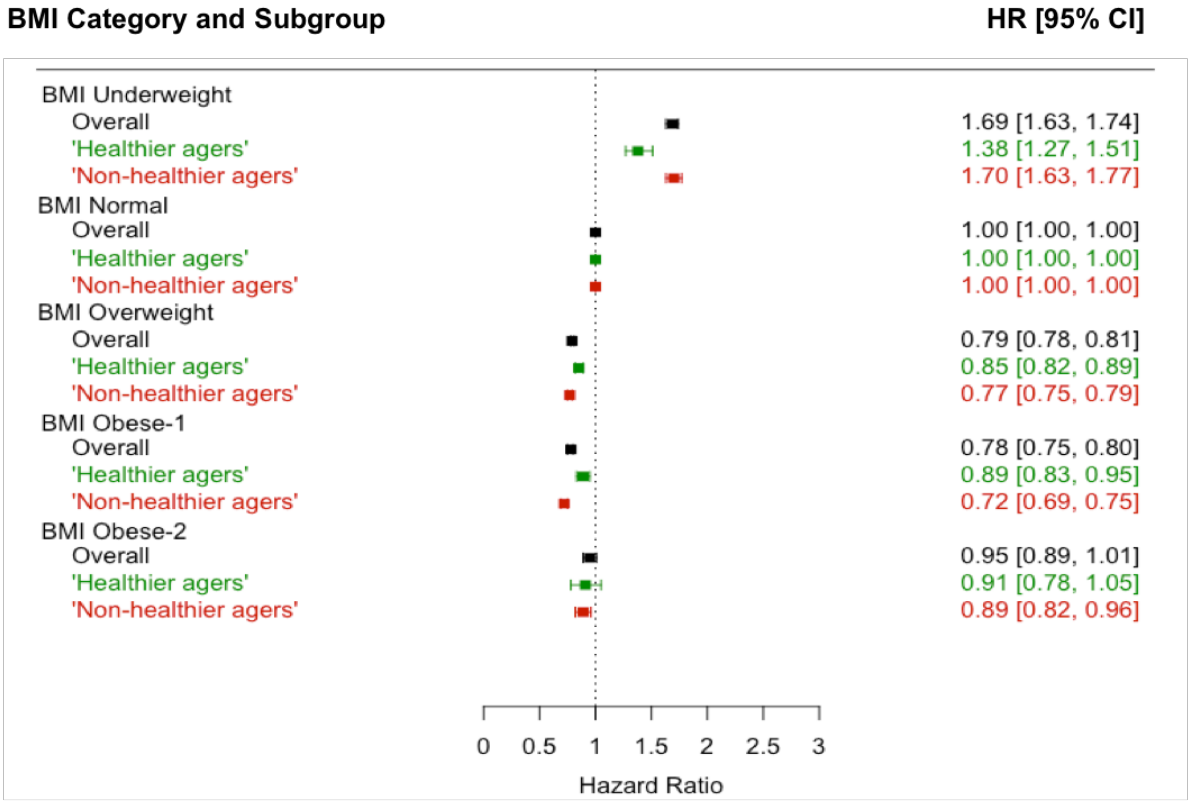
Note: 'Healthier agers' were non-smokers without recent cancer (within the previous five years excluding non-melanoma skin cancer), dementia, heart failure, or multi-morbidity and survived the first 3.9 years. 'Non-healthier' agers were smokers, those with recent cancer (within the previous five years excluding non-melanoma skin cancer), dementia, heart failure, and multi-morbidity.

Figure 4.5 | Hazard ratios (95% CI) for all-cause mortality by conventional BMI categories for those aged 75 to 84 years at baseline for the overall sample (**black**), 'healthier agers' (**green**) and 'non-healthier agers' (**red**) from the CPRD. Cox proportional hazards were adjusted for age, gender, alcohol status, smoking status, calendar year, and socioeconomic status



Note: 'Healthier agers' were non-smokers without recent cancer (within the previous five years excluding non-melanoma skin cancer), dementia, heart failure, or multi-morbidity and survived the first 3.9 years. 'Non-healthier' agers were smokers, those with recent cancer (within the previous five years excluding non-melanoma skin cancer), dementia, heart failure, and multi-morbidity.

Figure 4.6 | Hazard ratios (95% CI) for all-cause mortality by conventional BMI categories for those aged ≥85 years at baseline for the overall sample (**black**), 'healthier agers' (**green**) and 'non-healthier agers' (**red**) from the CPRD. Cox proportional hazards were adjusted for age, gender, alcohol status, smoking status, calendar year, and socioeconomic status



Note: 'Healthier agers' were non-smokers without recent cancer (within the previous five years excluding non-melanoma skin cancer), dementia, heart failure, or multi-morbidity and survived the first 3.9 years. 'Non-healthier' agers were smokers, those with recent cancer (within the previous five years excluding non-melanoma skin cancer), dementia, heart failure, and multi-morbidity.

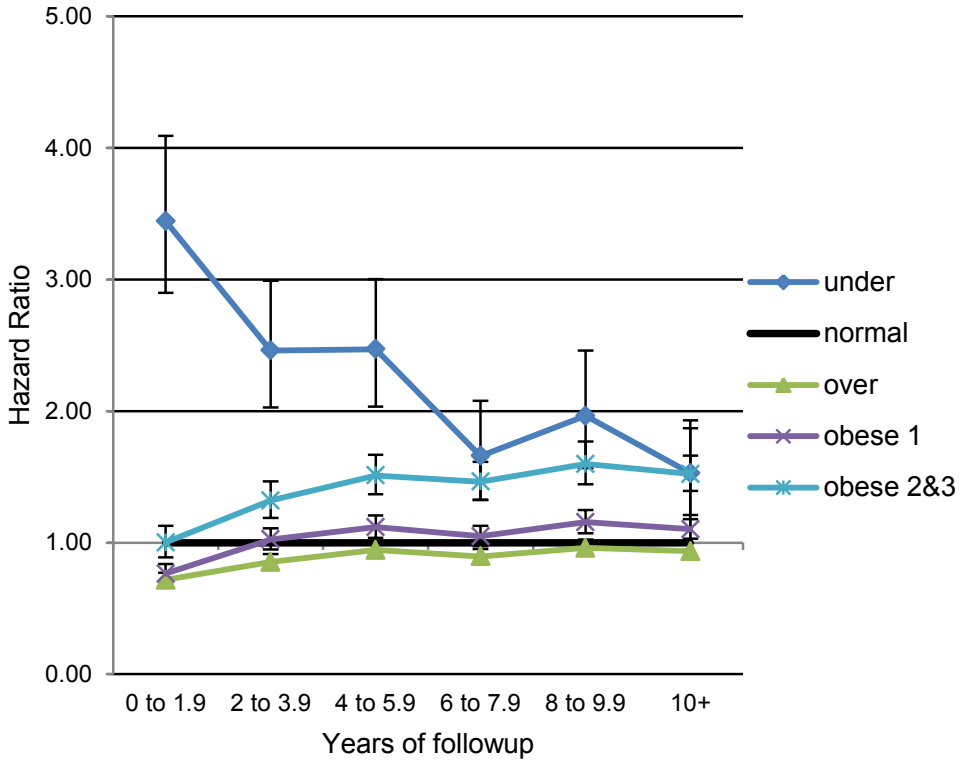
4.5.6. Accounting for confounding and follow-up period

To account for confounders, current smokers plus patients with multi-morbidity, recent cancer at baseline (within the previous five years, excluding non-melanoma skin cancer), dementia, or heart failure (i.e. the factors most strongly associated with prior weight loss – see methods and **Table 4.2**) were excluded to yield a 'healthier agers' group. To clarify the length of follow-up to exclude, mortality risks were plotted for two-year time periods to avoid the biasing effects of serious disease present at baseline (**Figure 4.7** and supplementary material Table S4.4). For the age group 65 to 74 years at baseline, those within the BMI Obese-1 range had a survival advantage during the first two years of follow-up and this reversed after two years. Mortality risks for the other BMI categories showed similar patterns, all reaching apparent stability after four years (except for the BMI Underweight range which stabilized after six years). For the 'healthier agers' subgroup, persons that died within the first 3.9 years of follow-up were excluded to enable estimation of stable longer term mortality hazards.

4.5.7. 'Healthier agers'

Figures 4.2-4.6 present the mortality risks for each 'healthier agers' age-group by the conventional BMI categories for the complete cases, shown in **green** (supplementary material Table S4.5). Using the conventional BMI categories there were increased mortality risks for those within the BMI Obese-1 range up to age 74 years: in the 65 to 69 age group this was HR 1.17 (CI 1.11, 1.23) relative to those within the conventional BMI Normal range. In the conventional BMI Overweight range for those aged 65 to 69 years at baseline, the apparent protective effect also reversed to yield a non-significant difference relative to those within the conventional BMI Normal range (HR 0.96 CI 0.92, 1.01). The mortality risks for the 'healthier agers' within the BMI Obese-2 and BMI Obese-3 (**green**) were accentuated compared to the overall sample (**black**) for each of the age groups up to age 84 years.

Figure 4.7 | Hazard ratios for mortality by conventional BMI category and length of follow-up in those aged 65 to 74 years at baseline, compared to those within the conventional BMI Normal range from the CPRD



4.5.8. 'Non-healthier agers'

Figures 4.2-4.6 present the mortality risks for each 'non-healthier agers' age-group by the conventional BMI categories for the complete cases, shown in **red** (supplementary material Table S4.6). Mortality risks were estimated for those excluded from the 'healthier agers' subgroup, i.e. smokers plus patients with multi-morbidity, heart failure, dementia, or recent cancer. For the 65 to 69 years 'non-healthier agers' group (*n* = 127,204 with 24,169 deaths), those within the BMI Overweight, BMI Obese-1, and BMI Obese-2 ranges had reduced mortality risks relative to those within the conventional BMI Normal range (BMI Overweight HR 0.72 CI 0.70, 0.74; BMI Obese-1 HR 0.76 CI 0.73, 0.79; BMI Obese-2 HR 0.84 CI 0.80, 0.89). The mortality risks were raised in the BMI Obese-3 range HR 1.14 (CI 1.06, 1.22). A similar pattern of lower mortality risks for the BMI Overweight, BMI Obese-1 and BMI Obese-2 ranges was observed across the other age-groups.

Sensitivity analyses

Mortality risks remained increased for the 'healthier agers' within the BMI Obese-1, BMI Obese-2, and BMI Obese-3 ranges relative to those within the conventional BMI Normal range up to age 74 years after additional adjustment for physical activity level (data available for 55.3% patients aged 60 to 64; 55.6% aged 65 to 69; 56.1% aged 70 to 74; 55.8% aged 75 to 84; and 55.9% ≥85 years) (**Table 4.4**). The mortality risk for the BMI Obese-1 range for those aged 75 to 84 years and for those aged ≥85 years was not significantly different from those within the conventional BMI Normal range.

Several studies have reported paradoxical BMI associations for both cardiovascular disease and type 2 diabetes (Niedziela, *et al*., 2014; Costanzo, *et al*., 2015). In additional analyses patients with a previous diagnosis of cardiovascular disease namely angina, myocardial infarction, or stroke were excluded (**Table 4.5).** In further analyses those with cardiovascular disease and/or type 2 diabetes were excluded (**Table 4.6**). Mortality risks showed a similar pattern to the main analysis for the 'healthier agers' after further excluding those with cardiovascular disease. After excluding those with cardiovascular disease or type 2 diabetes, some of the mortality risks reduced. For those aged 65 to 74 years, the BMI Overweight range was associated with a reduced mortality risk relative to those within the BMI Normal range. For those aged 70 to 74 years, the BMI Obese-1 range was not significantly different to those within the BMI Normal range. For those aged 75 to 84 years, the BMI Obese-1 range was associated with a reduced mortality risk relative to those within the BMI Normal range.

Table 4.4 | Hazard ratios for mortality by BMI category for 'healthier agers' by age group with additional adjustment for physical activity using the CPRD

	Age group (years)				
	60 to 64 [a]	**65 to 69** [a]	**70 to 74** [a]	**75 to 84** [a]	**≥85** [a]
Underweight 14.0 to <18.5	35/410 2.53 (1.83, 3.51)	51/365 2.00 (1.52, 2.63)	120/487 1.63 (1.36, 1.95)	462/882 1.73 (1.58, 1.90)	292/410 1.50 (1.33, 1.69)
Normal weight 18.5 to <25.0	826/18925 1.00	1477/17109 1.00	2611/15717 1.00	7108/19576 1.00	2892/5089 1.00
Overweight 25.0 to <30.0	1400/29287 1.01 (0.93, 1.10)	2480/26505 0.99 (0.93, 1.06)	3658/23590 0.90 (0.86, 0.95)	6987/22230 0.90 (0.87, 0.93)	1856/3595 0.87 (0.82, 0.92)
Obese-1 30.0 to < 35.0	773/14071 1.21 (1.10, 1.33)	1265/12110 1.19 (1.10, 1.28)	1739/9980 1.08 (1.02, 1.15)	2455/8025 0.96 (0.92, 1.01)	459/970 0.91 (0.82, 1.00)
Obese- 2 35.0 to < 40.0	312/4523 1.66 (1.46, 1.89)	360/ 3465 1.33 (1.19, 1.49)	493/2687 1.26 (1.14, 1.38)	580/1834 1.12 (1.03, 1.22)	101/182 0.86 (0.71, 1.05)
Obese-3 ≥40.0	178/1830 2.64 (2.25, 3.10)	222/1325 2.23 (1.94, 2.57)	188/860 1.75 (1.51, 2.03)	162/479 1.32 (1.13, 1.53)	

[a] Cell contents: events/number, HR (95% CI)

Note: 'Healthier agers' were non-smokers without recent cancer (within the previous five years excluding non-melanoma skin cancer), dementia, heart failure, or multi-morbidity and survived the first 3.9 years. Cox proportional hazards models were adjusted for age, gender, alcohol use, smoking, calendar year, and socioeconomic status. For the age ≥85 years age group the BMI Obese-2 and BMI Obese-3 were combined.

Table 4.5 | Hazard ratios for mortality by BMI category for 'healthier agers' by age group with patients diagnosed previously with angina, myocardial infarction, or stroke excluded using the CPRD

	Age group (years)				
	60 to 64 [a]	65 to 69 [a]	70 to 74 [a]	75 to 84 [a]	≥85 [a]
Underweight 14.0 to <18.5	63/730 2.21 (1.72, 2.85)	114/700 2.19 (1.81, 2.64)	254/875 1.95(1.72, 2.22)	832/1554 1.59 (1.48, 1.70)	502/680 1.40 (1.28, 1.54)
Normal weight 18.5 to <25.0	1472/31911 1.00	2577/28001 1.00	4395/25224 1.00	11733/30715 1.00	4645/7617 1.00
Overweight 25.0 to <30.0	2585/49050 1.04 (0.97, 1.11)	4129/42768 0.96 (0.92, 1.01)	5979/36305 0.91 (0.87, 0.94)	11326/33776 0.89 (0.87, 0.91)	2906/5232 0.85 (0.81, 0.89)
Obese-1 30.0 to < 35.0	1509/24404 1.24 (1.16, 1.34)	2252/20278 1.17 (1.11, 1.204)	2862/15956 1.06 (1.01, 1.11)	4111/12401 0.97 (0.94, 1.01)	740/1456 0.86 (0.80, 0.93)
Obese- 2 35.0 to < 40.0	622/8010 1.72 (1.57, 1.89)	741/ 6071 1.41 (1.30, 1.53)	912/4480 1.36 (1.26, 1.46)	1011/2952 1.14 (1.07, 1.22)	153/263 0.90 (0.76, 1.06)
Obese-3 ≥40.0	366/3352 2.58 (2.30, 2.90)	409/2340 2.21 (1.99, 2.45)	331/1384 1.82 (1.63, 2.04)	288/755 1.55 (1.38, 1.75)	

[a] Cell contents: events/number, HR (95% CI)

Note: 'Healthier agers' were non-smokers without recent cancer (within the previous five years excluding non-melanoma skin cancer), dementia, heart failure, or multi-morbidity and survived the first 3.9 years. Cox proportional hazards models were adjusted for age, gender, alcohol use, smoking, calendar year, and socioeconomic status. For the age ≥85 years age group the BMI Obese-2 and BMI Obese-3 were combined.

Table 4.6 | Hazard ratios for mortality by BMI category for 'healthier agers' by age group with patients diagnosed previously with angina, myocardial infarction, stroke or type 2 diabetes excluded using the CPRD

	Age group (years)				
	60 to 64 [a]	65 to 69 [a]	70 to 74 [a]	75 to 84 [a]	≥85 [a]
Underweight 14.0 to <18.5	63/712 2.36 (1.83, 3.04)	109/672 2.26 (1.87, 2.75)	247/838 2.05 (1.80, 2.33)	811/1511 1.62 (1.51, 1.74)	476/649 1.39 (1.26, 1.53)
Normal weight 18.5 to <25.0	1349/30541 1.00	2331/26351 1.00	3919/23330 1.00	10887/28575 1.00	4324/7057 1.00
Overweight 25.0 to <30.0	2239/45084 1.02 (0.96, 1.10)	3502/38402 0.94 (0.89, 0.99)	5095/31956 0.90 (0.87, 0.94)	10044/29987 0.88 (0.86, 0.91)	2558/4597 0.84 (0.80, 0.88)
Obese-1 30.0 to < 35.0	1237/21281 1.21 (1.12, 1.31)	1800/17258 1.13 (1.06, 1.20)	2279/13358 1.02 (0.97, 1.08)	3466/10530 0.95 (0.91, 0.98)	606/1212 0.82 (0.75, 0.89)
Obese- 2 35.0 to < 40.0	499/6687 1.72 (1.55, 1.91)	565/ 4892 1.36 (1.24, 1.49)	694/3538 1.31 (1.21, 1.42)	809/2329 1.12 (1.04, 1.21)	123/210 0.87 (0.73. 1.04)
Obese-3 ≥40.0	263/2628 2.41 (2.10, 2.75)	286/1783 2.01 (1.78, 2.28)	233/1012 1.70 (1.49, 1.94)	230/575 1.57 (1.37, 1.78)	

[a] Cell contents: events/number, HR (95% CI)

Note: 'Healthier agers' were non-smokers without recent cancer (within the previous five years excluding non-melanoma skin cancer), dementia, heart failure, or multi-morbidity and survived the first 3.9 years. Cox proportional hazards models were adjusted for age, gender, alcohol use, smoking, calendar year, and socioeconomic status. For the age ≥85 years age group the BMI Obese-2 and BMI Obese-3 were combined.

4.6. Discussion

Several analyses have reported that older persons within the BMI Overweight and BMI Obese-1 ranges have better or similar survival to those within the conventionally defined BMI Normal range, apparently undermining the scientific rationale for some responses to the global obesity epidemic. In models ignoring suggested confounding (i.e. smokers or conditions associated with weight loss) similar paradoxical estimates for BMI and mortality were obtained. Severely paradoxical estimates for those with conditions strongly associated with weight loss were also obtained. However, in models focused on non-smoking relatively healthy older people (i.e. free of cancer, dementia, heart failure, and multi-morbidity) - the results showed a reversal of the mortality risk with no sign of protective effects for those within the BMI Obese-1 range and aged 60 to 84 years. There was an elevated mortality risk for those within the BMI Obese-1 range for mortality compared to those within the conventional BMI Normal range up to age 74 years.

For 'healthier agers', the mortality risk for the BMI Overweight group was not significantly different compared to those within the conventional BMI Normal range for the two youngest age groups (60 to 64 years; 65 to 69 years). Reduced mortality risks were found for those aged ≥70 years even after the exclusion of smokers and those with diseases associated with major weight loss. Several previous analyses have reported that the BMI associated with minimum mortality risk lies within the BMI Overweight range (Flicker *et al.*, 2010; van Uffelen *et al.*, 2010; de Hollander *et al.*, 2012 b; Cheng *et al.*, 2016). This could be due to the BMI referent group (see section 4.6.4), higher BMI exerting a protective effect during periods of stress and persons within the BMI Overweight range being treated and monitored more closely for vascular risk factors, thus lessening the effect on mortality (**Chapter 1**). Furthermore, as highlighted in **Chapter 1**, BMI does not measure the body compositional changes with ageing i.e. the loss of muscle mass and function (sarcopenia), the increase in fat mass, and the redistribution of fat mass. Sarcopenia has been shown to be associated with increased mortality risks, which will not be captured by BMI (Hirani, *et al*., 2015; Brown, *et al*., 2016). Additionally, central adiposity has been shown to be associated with an increased mortality risk, again not measured by BMI (de

Hollander, *et al.*, 2012 a). These body compositional changes will be accentuated in the older age-groups, and thereby the BMI Overweight range could appear to be protective. The use of alternative measures of adiposity and body composition singularly and jointly will be assessed in **Chapters 7** and **8**.

Interestingly, after excluding persons with a previous diagnosis of angina, myocardial infarction, stroke or type 2 diabetes from the 'healthier agers' age-groups, the mortality risks for the BMI Obese-1 relative to those within the conventional BMI Normal range became non-significant for those aged 70 to 74 years, and significantly reduced for those aged 75 to 84 years. There was a reduced mortality risk for the BMI Overweight range for the age-group 65 to 69 years. However, these findings need to be interpreted cautiously, as these exclusionary criteria is more likely to affect the higher BMI values, possibly inducing a selection bias. Persons within the BMI Overweight and BMI Obese ranges without diabetes, coronary heart disease or stroke, may thereby be treated and monitored more frequently for primary prevention of diseases, attenuating mortality risks.

4.6.1. Comparison to previous literature

The results presented in this chapter are difficult to compare with previous work, as most reports were based on smaller samples of older volunteers, with varying groups of BMI and varying follow-ups. Also, most reports relate to patients who were less exposed to modern cardiovascular and diabetes interventions. Ling Lu *et al* (2015) recently reported an analysis of 3.3 million patients admitted to Veterans Administration hospitals, and for those aged 60 to 69 years old found markedly lower hazard ratios for mortality for those with the BMI Obese-1 range compared to those within the BMI Normal range (Lu *et al.*, 2015). Using pooled data from 19 studies, Berrington de Gonzalez *et al* (2010) reported similarly raised hazards for mortality in their Obese-1 older group. Their analysis was restricted to never smokers plus participants without cancer, heart disease or aged ≥85 years and had relatively small numbers of deaths to analyse in the older groups (2,754 and 546 deaths in the BMI Obese-1 range for those aged 60 to 69 and 70 to 84 years respectively) (Berrington de Gonzalez *et al.*, 2010).

4.6.2. Chapter analysis

Analysing electronic health records offers many advantages (e.g. large sample size, near complete population inclusion plus diagnosed disease and outcome ascertainment) but can introduce biases where recording of risk factors is incomplete or triggered by clinical events. This problem is somewhat reduced here as GPs were offered financial incentives to record cardiovascular risk measures in the time frame included in the analyses. The proportion of the potential sample with no BMI measure (38% of patients) compares well with non-response levels in most randomized trials and volunteer cohorts.

There is no data on whether the observed weight loss in this analysis was intentional or unintentional. A 1996 study in British primary care found that 18% of a sample aged 56 to 75 years experienced any perceived weight loss in the previous 4 years, with 4% stating this was for personal reasons only, unrelated to health concerns or physician advice (Wannamethee, Shaper and Lennon, 2005). The exclusion of the diseases empirically most closely associated with measured weight loss is systematic but incomplete. In the weight change subgroup for adults aged 65 to 69 years, 25.1% of the patients with >5 kg weight loss would remain in the analysis after excluding patients with recent cancer, dementia, heart failure, and multi-morbidity. This residual confounding may explain the paradoxical estimates in the oldest old and in the first years of follow-up, and may have resulted in some underestimation of the mortality risks for the BMI Overweight range.

The results I present in this chapter and **Chapter 3**, suggest that the claimed obesity risk paradox in later life is largely the erroneous result of failing to estimate risks separately for relatively healthy and already severely ill older groups.

In addition, obesity is associated with substantial excess disability (Angleman, Harris and Melzer, 2006; Gregg and Guralnik, 2007). Stenholm and colleagues reported that obese (BMI ≥30.0 kg/m^2) men and women aged 70 to 79 years from the Health, Aging and Body Composition Study had an increased risk of mobility limitation during a 6.5-year follow-up period (Stenholm *et al.*, 2010). Obese men and women aged ≥65 years from the English Longitudinal Study of Ageing were

reported to have an increased risk of self-reported difficulties with activities of daily living and with a measure of functional impairment during a five-year follow-up period (Lang *et al.*, 2008). The widespread publicity given to the claimed obesity risk paradox in the elderly is, therefore, inappropriate. Clinical advocacy of weight control for general health risk reduction was never claimed to be relevant to those already suffering from severe conditions associated with weight loss.

4.6.3. Strengths and limitations

I estimated mortality risks for the conventional WHO BMI categories across progressively older age groups and for subgroups of 'healthier agers' and 'non-healthier agers'. Using the CPRD allowed BMI mortality risk estimates to be derived for a near complete older population and permitted stratified analyses. I empirically tested the association of 15 major diagnoses with weight loss thus guiding which conditions to exclude. BMI mortality risk estimates were derived for two-year time segments which steered the length of follow-up to exclude as there is no consensus on the appropriate time lag. A major strength of this work is that even following sequential exclusions, the sample sizes for the age groups are much greater than those previously analysed (**Chapter 3**).

There are several limitations to this analysis reported in this chapter. One limitation of this analysis was that the outcome chosen was all-cause mortality. Therefore, risk estimates for the WHO BMI categories with specific causes of death or morbidity may differ to those presented in this chapter for all-cause mortality. As highlighted earlier the patients were predominately 'white' ethnicity and therefore the findings may not be generally applicable to other ethnic groups.

A further limitation of this analysis is the use of the Clinical Practice Research Datalink. As noted in the methods section (4.4), BMI records were available for 62% of the registered patients, and thus missing for 38%. As discussed in **Chapter 2**, the decision to take a height and weight measurement and to record these measures is dependent on the primary care practitioner, and could be captured during registration, opportunistically or during health checks. Height and weight may be recorded more often for patients with certain health conditions or

those with high cardiovascular risk, thus conferring a selection bias. Mortality risks may be inflated for higher BMI ranges if these patients are already at a heightened vascular risk. The UK Biobank could be used to address the limitations of using the CPRD, as most of the participants (99.4%) had height and weight recorded. This will be addressed in **Chapter 7**.

4.6.4. Future work

Additional work is needed to assess the choice of the BMI referent group; as noted in **Chapter 1** persons within the lower end of the conventional BMI Normal range may be at an increased risk for mortality which could distort mortality risk estimates for higher BMI values. In **Chapter 5** I use the CPRD database to re-define the BMI referent group by estimating the continuous BMI association with mortality. This revised groupwas used to estimate the BMI associations for mortality, incident Coronary Heart Disease, and Type 2 diabetes for progressively older groups of adults.

4.7. Conclusions

The obesity paradox in later life appears to be the erroneous result of combining mortality risks for relatively healthy, smokers, and already ill older groups. As obesity is associated with excess mortality in otherwise healthy non-smoking older people, up to and including those aged 74 years, assertions based on the claimed paradox against current obesity control efforts are misplaced.

Supplementary material for Chapter 4

List of Figures for supplementary material Chapter 4

List of Tables for supplementary material Chapter 4

Figure S4.1 | Directed acyclic graph (DAG) summarising causal influences on the association between BMI and mortality in older populations

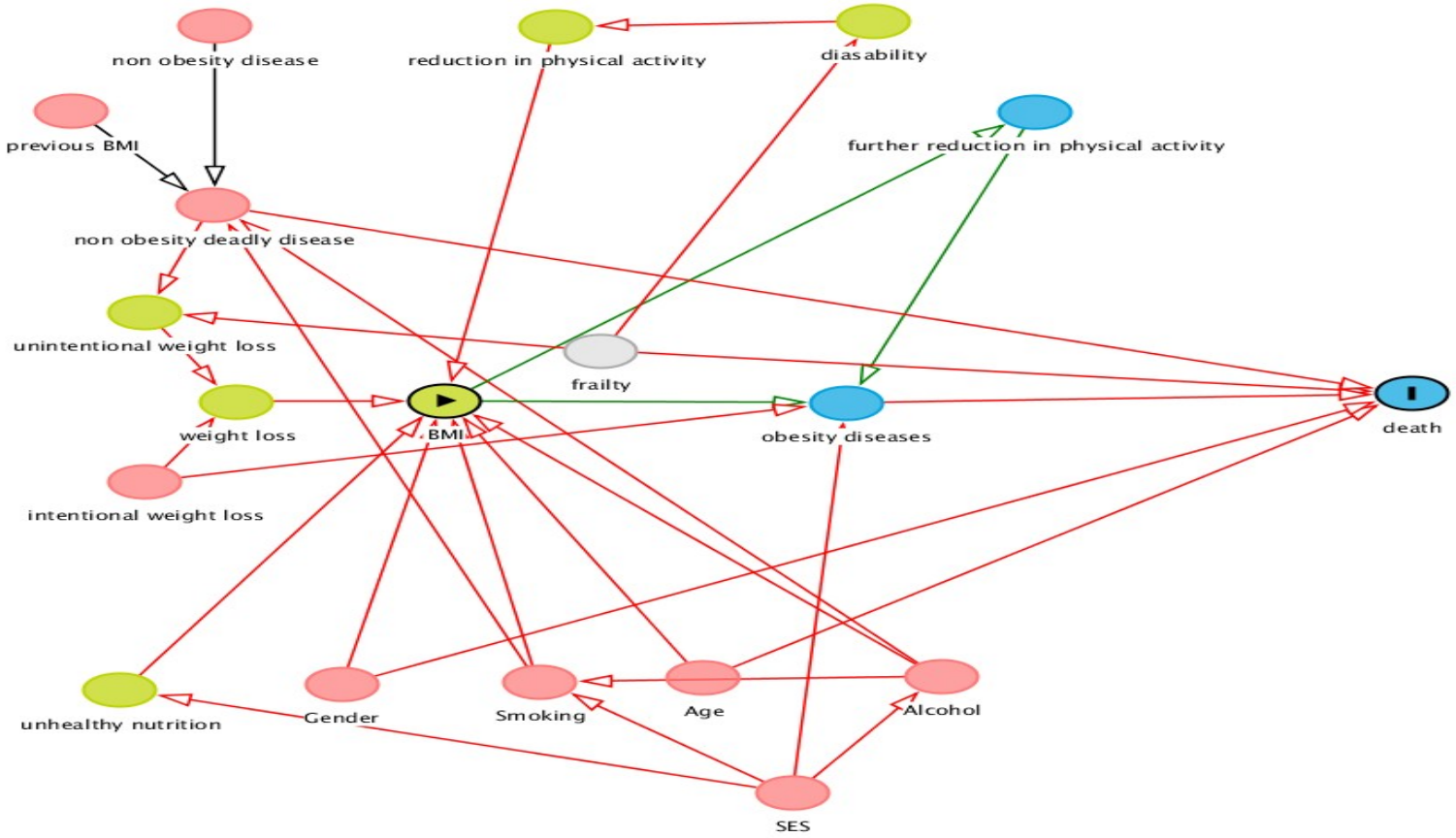


Table S4.1 | Detailed characteristics of the sample (including those with missing values), additional detail

	Age group (years)				
	60 to 64	**65 to 69**	**70 to 74**	**75 to 84**	**≥85**
n	402,604	367,358	313,644	337,807	119,140
Follow up years, mean (SD)	5.7 (3.9)	5.5 (3.9)	5.5 (3.8)	5.2 (3.6)	3.5 (2.7)
Age years, mean (SD)	61.8 (1.5)	66.7 (1.4)	71.6 (1.4)	77.8 (2.8)	87.3 (2.7)
Gender					
Females, n (%)	206,830 (51.4)	185,236 (50.4)	163,203 (52.0)	189,265 (56.0)	76,232 (64.0)
BMI (kg/m^2), mean (SD)	28.2 (5.5)	28.0 (5.3)	27.6 (5.1)	26.6 (4.9)	24.7 (4.6)
BMI (kg/m^2) (%)					
Underweight 14.0 to <18.5	4,869 (1.2)	4,946 (1.4)	5,729 (1.8)	10,497 (3.1)	8,854 (7.4)
Normal weight 18.5 to <25.0	110,633 (27.5)	102,079 (27.8)	93,536 (29.8)	123,241 (36.5)	57,770 (48.5)
Overweight 25.0 to <30.0	158,180 (39.3)	148,047 (40.3)	127,278 (40.6)	130,682 (38.7)	37,947 (31.9)
Obese-1 30.0 to < 35.0	85,252 (21.2)	76,398 (20.8)	61,537 (19.6)	54,144 (16.0)	11,740 (9.9)
Obese- 2 35.0 to < 40.0	29,831 (7.4)	25,189 (6.9)	18,699 (6.0)	14,722 (4.4)	2,317 (1.9)
Obese-3 ≥40.0	13,839 (3.4)	10,699 (2.9)	6,865 (2.2)	4,521 (1.3)	512 (0.4)

Table S4.1 continued

	60 to 64	65 to 69	70 to 74	75 to 84	≥85
Alcohol Status, n (%)					
Non-drinker	40,429 (10.0)	40,821 (11.1)	39,762 (12.7)	50,158 (14.9)	20,687 (17.4)
Current drinker	223,479 (55.5)	203,287 (55.3)	173,562 (55.3)	183,510 (54.3)	60,906 (51.1)
Ex drinker	11,470 (2.9)	12,274 (3.3)	11,911 (3.8)	13,474 (4.0)	6,546 (5.5)
Heavy drinker	68,883 (17.1)	59,064 (16.1)	43,456 (13.9)	35,156 (10.4)	9,358 (7.9)
Not recorded	58,343 (14.5)	51,912 (14.1)	44,953 (14.3)	55,509 (16.4)	21,643 (18.2)
Smoking Status, n (%)					
Never	165,490 (41.1)	147,568 (40.2)	127,943 (40.8)	145,449 (43.1)	55,641 (46.7)
Current smoker	133,278 (33.1)	114,534 (31.2)	88,700 (28.3)	78,298 (23.2)	21,557 (18.1)
Ex-smoker	91,988 (22.9)	95,112 (25.9)	87,764 (28.0)	100,297 (29.7)	37,304 (31.3)
Not recorded	11,848 (2.9)	10,144 (2.8)	9,237 (3.0)	13,763 (4.1)	4,638 (3.9)
Index of multiple deprivation quintiles, n (%)					
1 (least deprived)	92,939 (23.1)	84,024 (22.9)	70,495 (22.5)	74,565 (22.1)	26,216 (22.0)
2	99,704 (24.8)	92,073 (25.1)	78,381 (25.0)	83,500 (24.7)	29,548 (24.8)

Table S4.1 continued

	60 to 64	65 to 69	70 to 74	75 to 84	≥85
IMD quintiles continued 3	84,812 (21.1)	77,765 (21.2)	66,364 (21.2)	71,826 (21.3)	26,078 (21.9)
4	75,455 (18.7)	69,030 (18.8)	59,898 (19.1)	65,820 (19.5)	22,951 (19.3)
5	49,644 (12.3)	44,439 (12.1)	38,463 (12.3)	42,016 (12.4)	14,309 (12.0)
Not recorded	50 (0.0)	27 (0.0)	43 (0.0)	80 (0.0)	38 (0.0)
Diagnosed disease at baseline, n (%)					
Recent cancer (<5 years)	15,823 (3.9)	19,268 (5.3)	20,701 (6.6)	26,652 (7.9)	11,128 (9.3)
Dementia	860 (0.2)	1,474 (0.4)	2,932 (0.9)	10,036 (3.0)	11,640 (9.8)
Heart Failure	6,587 (1.6)	10,102 (2.8)	13,889 (4.4)	25,471 (7.5)	17,422 (14.6)
Diabetes	46,256 (11.5)	52,162 (14.2)	51,646 (16.5)	54,534 (16.1)	20,227 (17.0)
Coronary Heart Disease	22,875 (5.7)	28,297 (7.7)	30,944 (9.9)	39,650 (11.7)	19,076 (16.0)
Electronic frailty index (score of 6 or more), n (%)	17,056 (4.2)	26,719 (7.3)	37,136 (11.8)	61,925 (18.3)	41,759 (35.1)

Table S4.1 continued

	60 to 64	65 to 69	70 to 74	75 to 84	≥85
Weight stability (4 years prior to BMI record) subgroup, n (%)	201,013 (49.9)	201,089 (54.7)	1180,268 (57.5)	179,398 (53.1)	68,432 (57.4)
Weight stable (weight loss or gain of 0 to <5.0 kg) in subgroup	150,262 (74.8)	153,899 (76.5)	141,901 (78.7)	140,892 (78.5)	51,191 (74.8)
Weight loss of ≥5 kg in subgroup	19,884 (9.9)	20,505 (10.2)	119,021 (10.6)	22,143 (12.3)	12,634 (18.5)
Weight gain of ≥5 kg in subgroup	30,867 (15.4)	26,685 (13.3)	19,346 (10.7)	16,363 (9.1)	4,607 (6.7)

Table S4.2 | Distribution of deaths for the complete cases for each age group and 'healthier agers' subgroups and the overall sample

	Age group (years)				
	60 to 64 [a]	**65 to 69** [a]	**70 to 74** [a]	**75 to 84** [a]	**≥85** [a]
Complete cases - (no exclusions and all follow up)	29025/340753 (8.5)	40815/312352 (13.1)	55769/265912 (21.0)	105863/278422 (38.0)	53883/96498 (55.8)
'Healthier agers' (complete cases)	7363/124960 (5.9)	11684/109560 (10.7)	17217/95001 (18.1)	34437/94957 (36.3)	10789/18341 (58.8)
Overall sample (including non-complete cases)	34358/402604 (8.5)	48442/367358 (13.2)	66772/313644 (21.3)	130198/337807 (38.5)	67814/119140 (56.9)
'Healthier agers' (including non-complete cases)	9095/151736 (6.0)	14289/132477 (10.8)	21062/115155 (18.3)	42459/117003 (36.3)	13333/22526 (59.2)

[a] Cell contents: events/number, (%)
Note: Complete cases were patients without missing values for alcohol status, smoking, or Index of Multiple Deprivation. 'Healthier agers' subgroup excluded current smokers plus patients with multi-morbidity, heart failure, dementia, or recent cancer at baseline and first 3.9 years of follow-up.

Table S4.3 | Distribution of deaths by BMI category and age-group for complete cases

BMI categories	Age group (years)				
	60 to 64 [a]	65 to 69 [a]	70 to 74 [a]	75 to 84 [a]	≥85 [a]
Underweight 14.0 to <18.5	1014/3882	1296/3917	2004/4443	4944/7692	4589/6260
Normal weight 18.5 to <25.0	8559/93428	12122/86315	18211/78498	43203/100107	27731/46396
Overweight 25.0 to <30.0	10060/135154	14968/126911	20895/109126	38209/109431	15990/31720
Obese-1 30.0 to < 35.0	5832/72102	8138/64981	10125/52292	14494/45264	4474/9823
Obese-2 35.0 to < 40.0	2303/24888	2790/21247	3246/15827	3796/12201	1099/2299
Obese-3 ≥40.0	1257/11299	1501/8981	1288/5726	1217/372	

[a] Cell contents: events/number

Table S4.4 | Hazard ratios for mortality by BMI category and length of follow-up for those aged 65 to 74 years at baseline

	Time segment (years)					
BMI categories	**0 to 1.9** [a]	**2 to 3.9** [a]	**4 to 5.9** [a]	**6 to 7.9** [a]	**8 to 9.9** [a]	**≥10** [a]
Underweight	145/2357	110/1785	109/1375	79/1047	80/737	74/446
14.0 to <18.5	3.45 (2.90, 4.09)	2.47 (2.03, 2.99)	2.46 (2.03, 3.00)	1.63(1.32, 2.08)	1.97 (1.57, 2.46)	1.54 (1.21, 1.93)
Normal weight	1401/75164	1537/59794	1562/47287	1735/37162	1561/27016	2098/17383
18.5 to <25.0	1.00	1.00	1.00	1.00	1.00	1.00
Overweight	1567/109864	2039/88649	2271/70088	2380/54845	2316/40185	3104/26058
25.0 to <30.0	0.72 (0.67, 0.77)	0.85 (0.80, 0.91)	0.94 (0.89, 1.01)	0.89(0.84, 0.95)	0.96 (0.90, 1.02)	0.95 (0.88, 0.99)
Obese-1	736/50979	1063/40666	1150/31670	1166/24227	1154/17518	1497/11174
30.0 to < 35.0	0.76 (0.70, 0.84)	1.02 (0.95, 1.11)	1.12 (1.04, 1.21)	1.04 (0.97, 1.13)	1.15 (1.07, 1.25)	1.11 (1.03, 1.18)
Obese-2 & 3	342/20703	476/16094	534/12220	541/9075	514/6356	659/3954
≥35.0	1.00 (0.89, 1.13)	1.31 (1.19, 1.47)	1.53 (1.37, 1.67)	1.46 (1.33, 1.61)	1.60 (1.44, 1.77)	1.51 (1.39, 1.66)

[a] Cell contents: events/number, (%)
Adjusted for age, gender, alcohol status, smoking status, calendar year, and Index Multiple of Deprivation. Current smokers, patients with cancer (last 5 years), dementia, heart failure, and multi-morbidity were excluded.

Table S4.5 | Distribution of deaths by BMI category and age-group for 'healthier agers' complete cases

BMI category	Age group (years)				
	60 to 64 [a]	65 to 69 [a]	70 to 74 [a]	75 to 84 [a]	≥85 [a]
Underweight 14.0 to <18.5	69/767	124/744	284/958	940/1728	581/791
Normal weight 18.5 to <25.0	1617/33431	2906/30094	5095/28083	13732/35240	5584/9113
Overweight 25.0 to <30.0	2872/52376	4745/46988	7071/41247	13404/39362	3521/6360
Obese-1 30.0 to < 35.0	1714/26177	2602/22475	3351/18118	4842/14379	915/1758
Obese-2 35.0 to < 40.0	691/8601	844/6685	1035/5031	1176/3379	188/319
Obese-3 ≥40.0	400/3608	463/2574	381/1564	343/869	

[a] Cell contents: events/number, (%)
'Healthier agers' excluded current smokers, patients with cancer (last 5 years), dementia, heart failure, multi-morbidity, and those who died within the first 3.9 years. In the ≥85 group obese 2 and obese 3 are combined.

Table S4.6 | Distribution of deaths by BMI category and age-group for complete cases of patients excluded from the 'healthier agers' sub group

	Age group (years)				
BMI category	**60 to 64** [a]	**65 to 69** [a]	**70 to 74** [a]	**75 to 84** [a]	**≥85** [a]
Underweight 14.0 to <18.5	877/2502	1070/2526	1489/2780	3201/4586	2928/3976
Normal weight 18.5 to <25.0	6023/38044	7835/35333	10756/33451	22826/45108	16376/26784
Overweight 25.0 to <30.0	5921/50515	8327/48869	10990/43860	19219/48228	9553/18735
Obese-1 30.0 to < 35.0	3360/28401	4492/26763	5427/22895	7536/21679	2815/6196
Obese-2 35.0 to < 40.0	1330/10210	1582/9440	1809/7516	2107/6428	721/1543
Obese-3 ≥40.0	684/4893	863/4273	755/2990	709/2126	

[a] Cell contents: events/number, (%)
'Healthier agers' excluded current smokers, patients with cancer (last 5 years), dementia, heart failure, multi-morbidity, and those who died within the first 3.9 years. In the ≥85 group obese 2 and obese 3 are combined.

Chapter 5 Re-defining the BMI reference group for mortality for progressively older age groups using electronic health records

Table of Contents

List of Tables for Chapter 5

List of Figures for Chapter 5

5.1. Overview of chapter

This chapter, like **Chapter 4**, is partly based on my first author published paper:

> Bowman, K., Delgado, J., Henley, W.E., Masoli, J.A., Kos, K., Brayne, C., Thokala, P., Lafortune, L., Kuchel, G.A., Ble, A., & Melzer, D. (2017) Obesity in Older People With and Without Conditions Associated With Weight Loss : Follow-up of 955,000 Primary Care Patients. J Gerontol A Biol Sci Med Sci. Editor's Choice. 72(2): 203–209.

Much of the **results** and **discussion** are direct translations from this published article. Some sentences have been modified to make the sentences clearer and additional headings have been used. The methods section is more concise as reference has been made to the preceding chapter on how the variables were coded and categorised.

The abstract, introductory section and concluding remarks have been revised to emphasise the links throughout this thesis. Additionally, I have added some of the supplementary material into the main text. Furthermore, additional sections have been added to the discussion to show the links throughout this thesis.

5.2. Summary

Background: The obesity paradox refers to instances where mortality risks have been reported to be reduced or non-significant for older adults (aged ≥65 years) within the body mass index (BMI) defined Obese-1 range (30.0-34.9 kg/m^2) relative to those within the conventional BMI Normal range (18.5-24.9 kg/m^2). This is partly due to the pooling of relatively healthy adults, smokers, and already ill older groups. These estimates may still be distorted due to the choice of the BMI referent group.

Objective: To estimate the continuous BMI association with mortality, to use these associations to re-define the BMI referent range and to use this revised referent group to estimate the associations for mortality, incident coronary heart disease (CHD), and Type 2 diabetes.

Design: This analysis used primary care, hospital and death certificate electronic health records for registered populations aged ≥60 years in England from 1 January 2000 from the Clinical Practice Research Datalink (CPRD) to define a subset of patients as 'healthier agers'. 'Healthier agers' were non-smokers without conditions associated with weight loss and who survived the first 3.9 years of the follow-up period. Spline point models, Cox proportional hazards, and competing risks models were used with adjustment for age, gender, alcohol use, smoking history (never or former), calendar year, and socioeconomic status.

Results: For the 'healthier agers', the BMI mortality curve for those aged 65 to 69 years at baseline was U-shaped, with raised mortality risks at lower BMIs, a nadir between 23.0 and 26.9 kg/m^2 and steeply rising mortality risks for higher BMI values. In older age groups, mortality nadirs were at modestly higher BMIs (all <30.0 kg/m^2) and risk slopes at higher BMIs were less marked, becoming nonsignificant for those aged ≥85 years at baseline. Incidence of diabetes was raised for those within the BMI Obese-1 range at all ages and for CHD up to and including those aged 84 years, relative to those within the BMI 23.0-26.9 kg/m^2 range.

Conclusions: Obesity is associated with shorter survival plus higher incidence of coronary heart disease and type 2 diabetes in older populations for 'healthier agers', at least up to and including those aged 84 years. These results cast doubt on calls to revise obesity control policies based on the claimed risk paradox at older ages.

5.3. Introduction

In **Chapter 3** I showed that mortality risks were reduced for those within the BMI Obese-1 (30.0-34.9 kg/m^2), and BMI Overweight (25.0-29.9 kg/m^2) ranges relative to those within the conventional BMI Normal range (18.5-24.9 kg/m^2) in unrestricted analyses (e.g. no exclusion of smokers, conditions associated with weight loss or early deaths) for adults aged ≥65 years. Analyses which had simultaneously excluded smokers, early deaths, and those with conditions associated with weight loss showed increased mortality risks for those within the BMI Obese-1 and the BMI Overweight ranges relative to those within the BMI Normal range. The obesity paradox, which refers to the reduced/non-significant mortality risks for those within the BMI Obese-1 range, is in part due to the inclusion of smokers and those with conditions associated with weight loss. Furthermore, In **Chapter 4** I presented an analysis which used the Clinical Practice Research Datalink (CPRD) to estimate associations between the WHO BMI categories and mortality which further demonstrated that the pooling of relatively healthy adults, those who are already ill and smokers can distort mortality risk estimates.

For the analyses in **Chapter 4** I used the conventional BMI Normal range as the referent group. As discussed in **Chapter 1** the conventional BMI Normal range will consist of those who have consistently been within the BMI Normal range and active, current smokers, and those whose BMI has decreased due to conditions associated with weight loss. Thus, due to the heterogeneous group within the conventional BMI Normal range, mortality risk estimates could be distorted for higher BMI values. As noted in **Chapter 3,** increased mortality risks were found for those within the BMI Overweight and BMI Obese-1 ranges for analyses that had used simultaneous exclusions plus a narrower BMI reference group with a lower limit of 22.0 kg/m^2.

The meta-analysis conducted by Winter *et al*., (2014) showed increased mortality risks for those with BMI values <23.0 kg/m^2 relative to those within the BMI range 23.0-23.9 kg/m^2 for adults aged ≥65 years (Winter *et al.*, 2014). Furthermore, Aune *et al*., (2016) showed increased mortality risks for those with BMI values <21.0 kg/m^2 for non-smokers aged ≥65 years (Aune *et al.*, 2016). These analyses

indicate that adults within the lower end of the conventional BMI Normal range may have an elevated mortality risk. Furthermore, de Hollander *et al*., (2012) showed the importance of reporting both the associations between categories of BMI, and continuous measures of BMI, with mortality; whilst there was no association between BMI categories and mortality, an association with continuous measures of BMI with mortality was found for adults aged 70 to 75 years from the SENECA study with a maximum follow-up duration of 10 years. The BMI value associated with the lowest mortality risk was 27.1 kg/m^2 and there were increased mortality risks for BMI values <20.0 kg/m^2 (de Hollander *et al.*, 2012 b).

The association of BMI with mortality is important to assess, however, it is also important to consider other health outcomes. Coronary heart disease (CHD) was the second leading cause of deaths for adults residing in England and Wales in 2015, and it was the principal cause of death for males aged 65 to 74 years (Office of National Statistics, 2016). Furthermore, in 2015 type 2 diabetes affected 4.5 million people in the UK (Diabetes UK, 2016). There has been a paucity of studies which have reported recent estimates for incident coronary heart disease and diabetes using narrower age groups and utilising competing risk models (supplementary material Table S5.1-2 and Table S5.3-4, respectively).

In this chapter I aimed to re-define the BMI referent group by estimating the continuous BMI association with mortality. This new BMI referent group was used to estimate the BMI associations for mortality, incident CHD, and Type 2 diabetes using a large cohort of 'healthier agers' (aged ≥60 years). As highlighted by de Hollander *et al*., (2012) associations between BMI and mortality may be concealed using categorisation (de Hollander *et al.*, 2012 b). In this chapter, I aimed to address the contributions of the BMI referent group to the obesity paradox as well as estimating the associations between BMI with incident CHD and diabetes using competing risk models that account for mortality.

5.4. Methods

5.4.1. Study Population

Using a similar methodology to **Chapter 4,** de-identified electronic health records from CPRD which were linked to the Hospital Episode Statistics (HES) data (linkage available for England only) and the government's Office for National Statistics (ONS) were used. As emphasized in **Chapters 2** and **4**, registration with GPs is nearly complete in the UK. The CPRD diagnostic and outcome coding has generally high validity (Herrett *et al.*, 2010).

5.4.2. Patients

All patients with BMI records since the 1st January 2000 and registered with a CPRD practice at the time of measurement were included. Extreme values of BMI were excluded (<14.0 and > 56.5 kg/m^2) (*n* = 6,431).

5.4.3. 'Healthier agers'

The 'healthier agers' subgroup included non-smokers without conditions associated with weight loss and who survived the first 3.9 years of the follow-up period. The conditions excluded were cancer (except non-melanoma skin cancer) within the previous five years, dementia, heart failure, and a measure of multi-morbidity. These conditions had been empirically identified as being associated with weight loss in **Chapter 4**. The length of follow-up to exclude for early deaths had also been assessed in **Chapter 4**.

5.4.4. Exposures

The earliest age at which a BMI was recorded was calculated within age groups 60 to 64, 65 to 69, 70 to 74, 75 to 84, and 85 years and older. The first BMI record was included for each patient within each age-group as the study 'index'. The WHO BMI categories were used which have been reported previously in **Chapters 1** and **4**. The BMI Obese-2 and BMI Obese-3 ranges were combined in those aged ≥85 years as there were <200 patients. Additionally, in this analysis the BMI referent category was redefined and the revised BMI groups will be documented in the results section.

5.4.5. Lifestyle and socioeconomic variables

In **Chapter 4,** I reported on the hypothesised causal influences on the BMI association with mortality which was depicted in the Directed Acyclic Graph presented in supplementary material Figure S4.1. Covariates used were age, gender, alcohol use, smoking history (never or former), calendar year, and socioeconomic status. The definition and categorising of these covariates were detailed in **Chapters 2** and **4**.

5.4.6. Outcomes

Outcomes included incident Coronary Heart Disease (angina or myocardial infarction diagnoses) from ICD 10 coded hospital records, incident type 2 diabetes (from GP records or hospital) and mortality (from Office for National Statistics death certificate data).

5.4.7. Statistical analysis

Spline models with 4 knots were used to estimate non-linear associations between BMI and mortality. Cox proportional hazards models were used to estimate the associations between the revised BMI groups and mortality. Although it has been established that there is a linear relationship between BMI and CHD and diabetes, the revised BMI referent group was additionally used to maintain both consistency and enable comparisons of the associations between BMI and different health outcomes. Competing risks models (accounting for mortality) for CHD and diabetes events were used. The proportional hazards assumption was tested for each model using Schoenfeld residuals. Multivariate models were adjusted for age, gender, alcohol use, smoking history, calendar year, and socioeconomic status. The effective age of the BMI exposure group (Brenner, Gefeller and Greenland, 1993), defined as the number of additional years of ageing in the control group that would result in equivalent mortality risks to those experienced by the exposed group, was derived using the rate advancement periods approach. Interactions between gender and BMI categories were assessed. Sensitivity analyses were carried out which further adjusted for physical activity levels (where available), restricting the sample to those with a ‘white’ ethnicity record, restricting the analyses to those with measured weight change, and using multiple imputation for missing records. The

missing values for smoking and alcohol intake were imputed multiple times using the chained (mlogit) multinomial logistic regression approach. In further sensitivity analyses, the revised referent group was split into BMI high Normal (23.0 to <25.0 kg/m^2) and BMI low Overweight (25.0 to <27.0 kg/m^2). Analyses were carried out using Stata statistical software (version 13.1) and R statistical software (version 3.1.2.) with packages "pspline" (version 2.37-7) and "survival" (version 1.0-16).

5.5. Results

5.5.1. Baseline characteristics

The baseline characteristics of the 'healthier agers' with complete records for smoking, alcohol use, and socioeconomic status are presented in **Table 5.1** (supplementary material table S5.3 for the 'healthier agers' with incomplete records). The mean BMI was 28.2 kg/m^2 for those aged 60 to 64 years and 24.9 kg/m^2 for those aged ≥85 years at baseline. Substantial measured weight loss was present in 4.1% and 6.2% of the youngest and oldest groups, respectively.

5.5.2. BMI continuous associations with mortality

Spline point regression was used to estimate the mortality risks for continuous BMI. Models were adjusted for age, gender, smoking history, alcohol use, calendar year, and socioeconomic status. **Figures 5.1** to **5.5** present the BMI associations for each age group. For all ages, the lower end of the conventional BMI Normal range (18.5-22.9 kg/m^2) was associated with sharply rising mortality risks with reducing BMI. For those aged 60 to 64 years (**Figure 5.1**) or 65 to 69 years (**Figure 5.2**) at baseline the lowest mortality risks were between BMI 23.0 to 26.9 kg/m^2 (although higher in older groups). Mortality risks rise moderately between 27.0 to 29.9 kg/m^2 and steeply at higher BMIs in the obese range for the two youngest age groups. For the age groups 70 to 74 years (**Figure 5.3**) and 75 to 84 years (**Figure 5.4**) there were increased mortality risks across the BMI obese range.

Table 5.1 | Characteristics of the sample (complete cases with no missing data on model covariates) from the CPRD

	Age group (years)				
	60 to 64	**65 to 69**	**70 to 74**	**75 to 84**	**≥85**
n	124,960	109,560	95,001	94,957	18,341
Follow up years, mean (SD)	8.5 (3.0)	8.6 (3.0)	8.4 (2.8)	8.1 (2.7)	6.8 (2.1)
Age years, mean (SD)	61.9 (1.5)	66.8 (1.5)	71.8 (1.5)	77.9 (2.7)	87.0 (2.2)
Gender					
Females, n (%)	67,589 (54.1)	58,390 (53.3)	51,864 (54.6)	56,496 (59.5)	12,533 (68.3)
BMI (kg/m^2), mean (SD)	28.2 (5.1)	28.0 (4.9)	27.5 (4.7)	26.5 (4.5)	24.9 (4.2)
BMI (kg/m^2) (%)					
Underweight 14.0 to <18.5	767 (0.6)	744 (0.7)	958 (1.0)	1,728 (1.8)	791 (4.3)
Normal weight 18.5 to <25.0	33,431 (26.8)	30,094 (27.5)	28,083 (29.6)	35,240 (37.1)	9,113 (49.7)
Overweight 25.0 to <30.0	52,376 (41.9)	46,988 (42.9)	41,247 (43.4)	39,362 (41.5)	6,360 (34.7)
Obese-1 30.0 to < 35.0	26,177 (21.0)	22,475 (20.5)	18,118 (19.1)	14,379 (15.1)	1,758 (9.6)
Obese- 2 35.0 to < 40.0	8,601 (6.9)	6,685 (6.1)	5,031 (5.3)	3,379 (3.6)	319 (1.7)
Obese-3 ≥40.0	3,608 (2.9)	2,574 (2.4)	1,564 (1.7)	869 (0.9)	

Table 5.1 continued

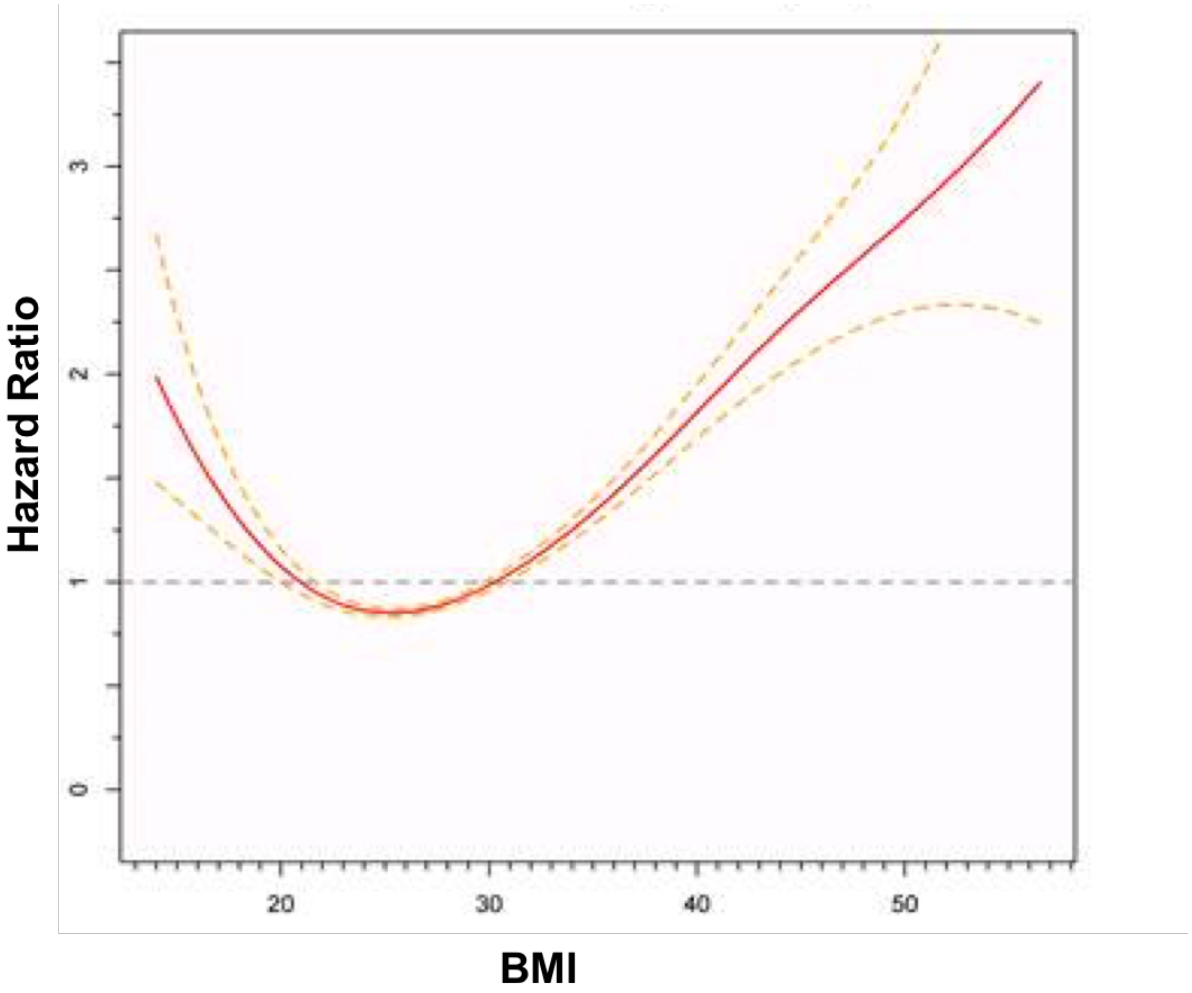
	60 to 64	65 to 69	70 to 74	75 to 84	≥85
Alcohol Status, n (%)					
Non-drinker	15,434 (12.4)	15,587 (14.2)	14,979 (15.8)	17,442 (18.4)	4,095 (22.3)
Current drinker	88,533 (70.9)	76,921 (70.2)	66,884 (70.4)	66,852 (70.4)	12,529 (68.3)
Ex drinker	2,510 (2.0)	2,554 (2.3)	2,435 (2.6)	2,701 (2.8)	639 (3.5)
Heavy drinker	18,483 (14.8)	14,498 (13.2)	10,703 (11.3)	7,962 (8.4)	1,078 (5.9)
Smoking Status, n (%)					
Never	81,242 (65.0)	69,151 (63.1)	59,165 (62.3)	59,057 (62.2)	11,784(64.3)
Ex-smoker	43,718 (35.0)	40,409 (36.9)	35,836 (37.7)	35,900 (37.8)	6,557 (35.8)
Index of multiple deprivation quintiles, n (%)					
1 (least deprived)	32,836 (26.3)	28,056 (25.6)	23,735 (25.0)	22,570 (23.8)	3,969 (21.6)
2	33,472 (26.8)	29,059 (26.5)	24,906 (26.2)	24,234 (25.5)	4,668 (25.5)
3	26,420 (21.1)	23,154 (21.1)	19,904 (21.0)	20,104 (21.2)	3,949 (21.5)
4	20,651 (16.5)	18,799 (17.2)	16,866 (17.8)	17,701 (18.6)	3,642 (19.9)
5	11,581 (9.3)	10,492 (9.6)	9,590 (10.1)	10,348 (10.9)	2,113 (11.5)

Table 5.1 continued

	60 to 64	65 to 69	70 to 74	75 to 84	≥85
Diagnosed disease at baseline, n (%)					
Diabetes	11,699 (9.4)	12,335 (11.3)	11,867 (12.5)	10,242 (10.8)	1,836 (10.0)
Coronary Heart Disease	4,870 (3.9)	5,775 (5.3)	6,188 (6.5)	6,399 (6.7)	1,336 (7.3)
Weight stability (4 years prior to BMI record) subgroup, n (%)	60,584 (48.5)	55,892 (51.0)	50,209 (52.9)	47,183 (49.7)	10,061 (55.9)
Weight stable (weight loss or gain of 0 to <5.0 kg) in subgroup	46,950 (77.5)	44,527 (79.7)	41,311 (43.5)	39,114 (82.9)	8,365 (83.1)
Weight loss of ≥5 kg in subgroup	5,071 (8.4)	4,483 (8.0)	3,826 (4.0)	4,091 (8.7)	1,142 (11.4)
Weight gain of ≥5 kg in subgroup	8,563 (14.1)	6,882 (6.3)	5,072 (12.3)	3,978 (8.4)	554 (5.5)

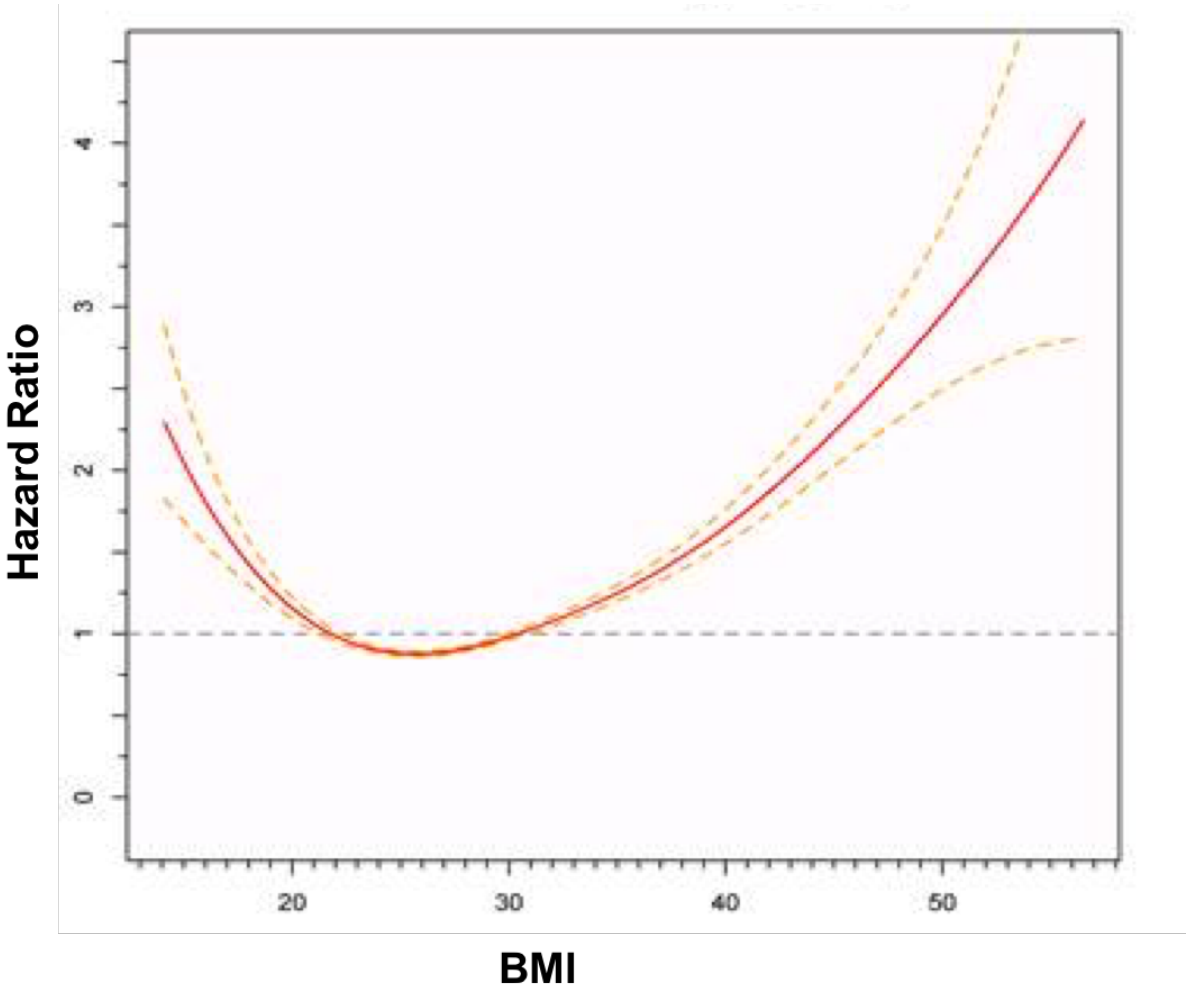
Note: 'Healthier agers' were defined as non-smokers, without recent cancer (within the five previous years except non-melanoma skin cancer), dementia, heart failure, or multi-morbidity and survived the first 3.9 years of follow-up

Figure 5.1 | Spline point estimates for BMI and mortality for 'healthier agers' aged 60 to 64 years at baseline using the CPRD



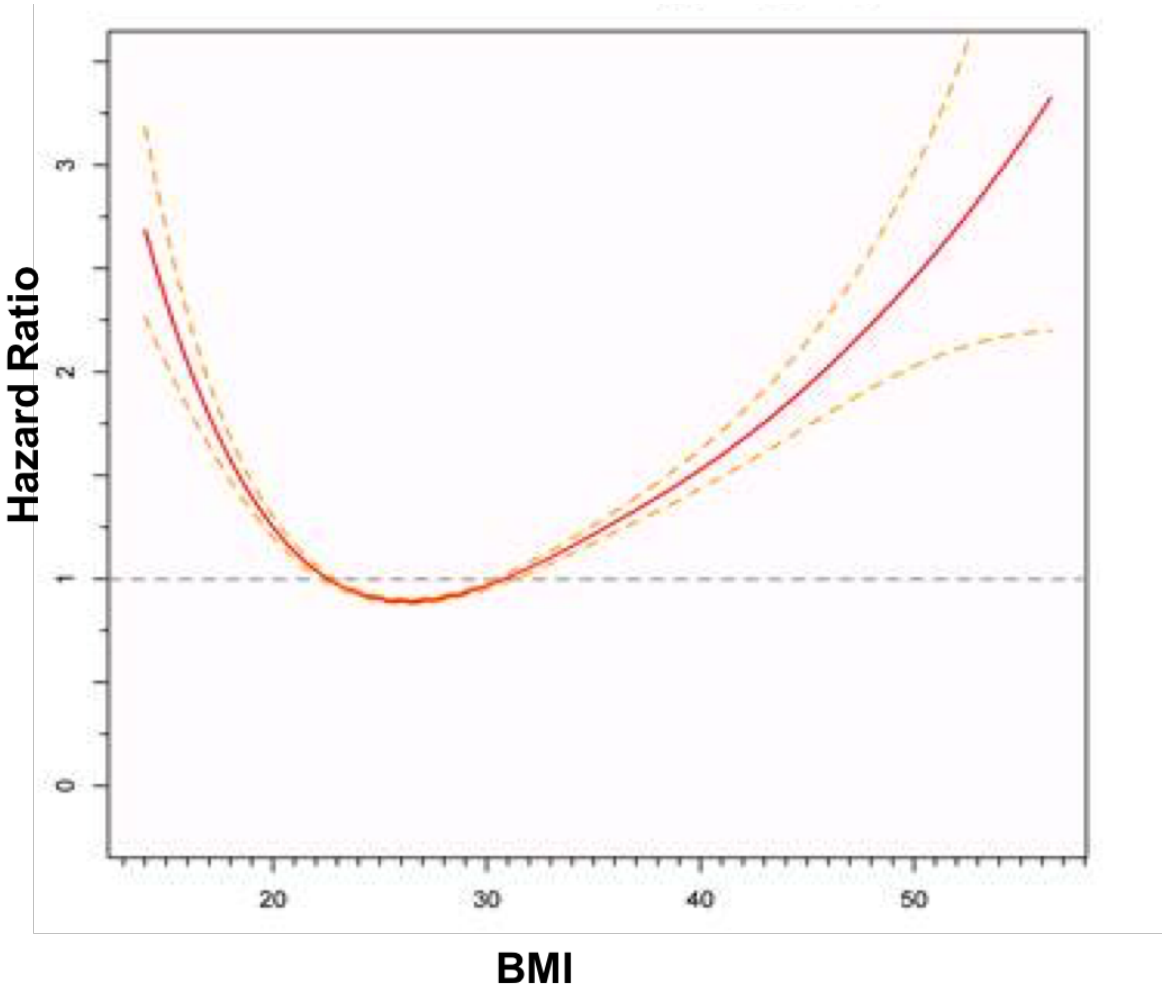
Note: 'Healthier agers' were defined as non-smokers, without recent cancer (within the five previous years except non-melanoma skin cancer), dementia, heart failure, or multi-morbidity and survived the first 3.9 years of follow-up. Models were adjusted for gender, alcohol use, smoking history, calendar year, and socioeconomic status. The line in red is the hazard ratio and the broken lines in yellow are the 95% confidence intervals.

Figure 5.2 | Spline point estimates for BMI and mortality for 'healthier agers' aged 65 to 69 years at baseline using the CPRD



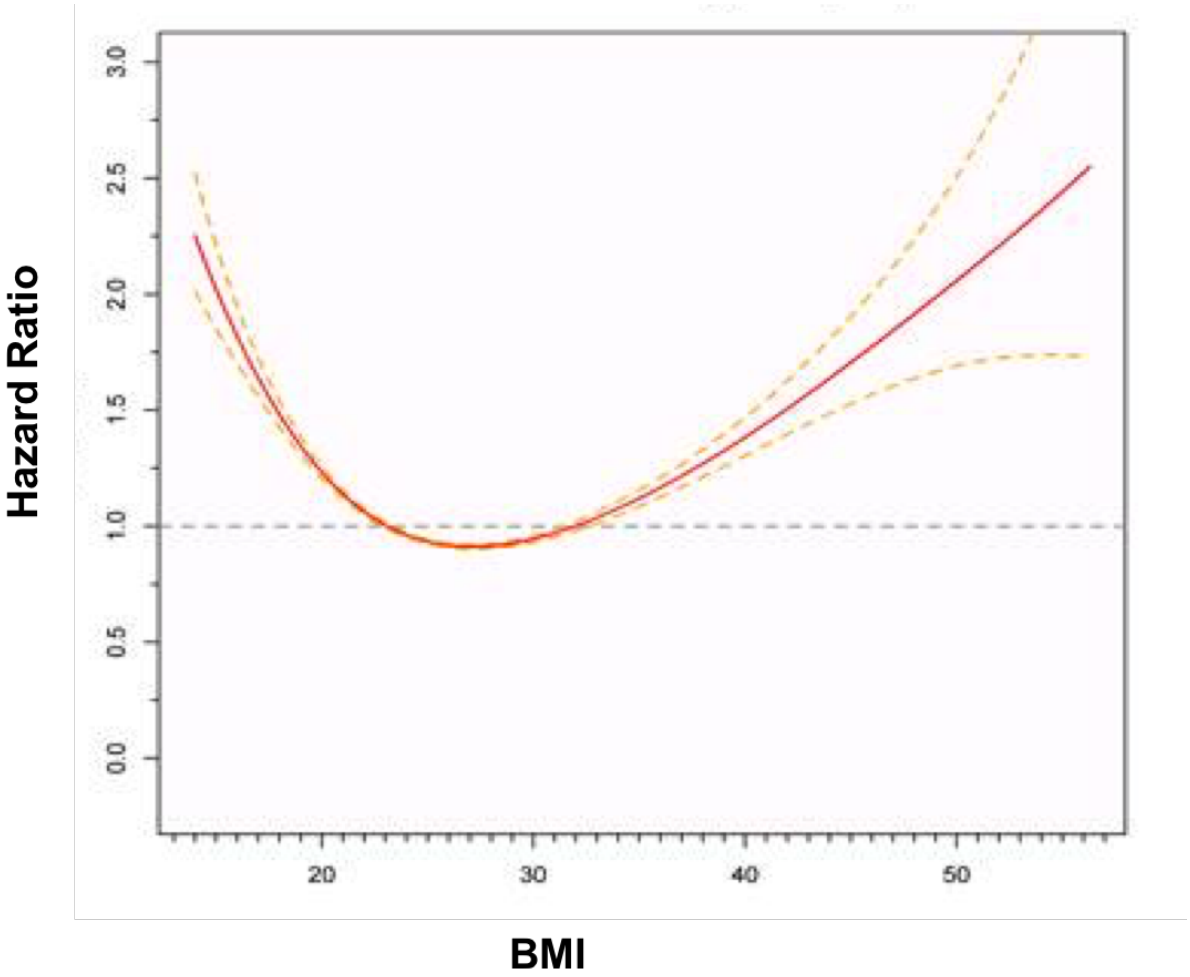
Note: 'Healthier agers' were defined as non-smokers, without recent cancer (within the five previous years except non-melanoma skin cancer), dementia, heart failure, or multi-morbidity and survived the first 3.9 years of follow-up. Models were adjusted for gender, alcohol use, smoking history, calendar year, and socioeconomic status. The line in red is the hazard ratio and the broken lines in yellow are the 95% confidence intervals.

Figure 5.3 | Spline point estimates for BMI and mortality for 'healthier agers' aged 70 to 74 years at baseline using the CPRD



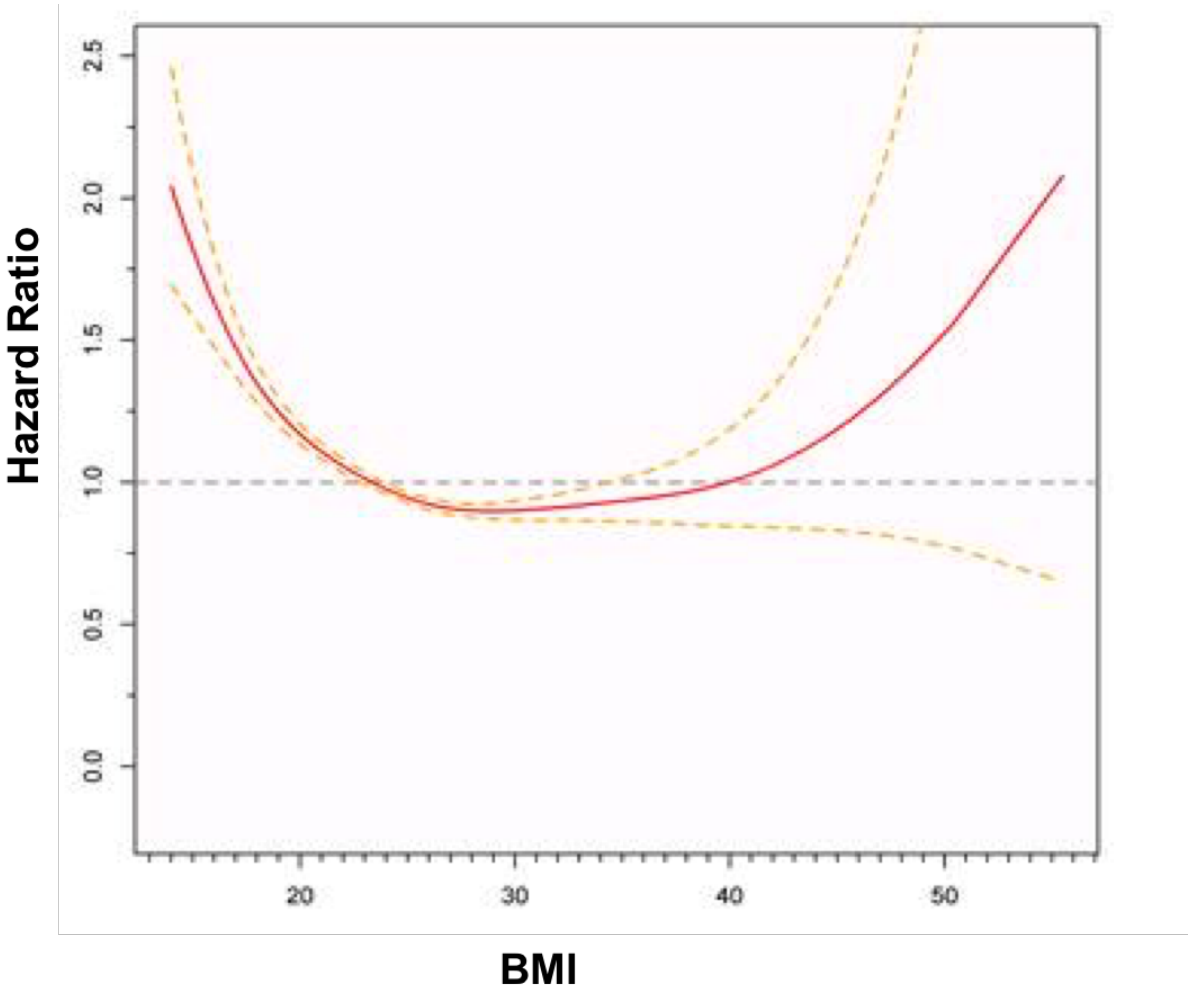
Note: 'Healthier agers' were defined as non-smokers, without recent cancer (within the five previous years except non-melanoma skin cancer), dementia, heart failure, or multi-morbidity and survived the first 3.9 years of follow-up. Models were adjusted for gender, alcohol use, smoking history, calendar year, and socioeconomic status. The line in red is the hazard ratio and the broken lines in yellow are the 95% confidence intervals.

Figure 5.4 | Spline point estimates for BMI and mortality for 'healthier agers' aged 75 to 84 years at baseline using the CPRD



Note: 'Healthier agers' were defined as non-smokers, without recent cancer (within the five previous years except non-melanoma skin cancer), dementia, heart failure, or multi-morbidity and survived the first 3.9 years of follow-up. Models were adjusted for gender, alcohol use, smoking history, calendar year, and socioeconomic status. The line in red is the hazard ratio and the broken lines in yellow are the 95% confidence intervals.

Figure 5.5 | Spline point estimates for BMI and mortality for 'healthier agers' aged ≥85 years at baseline using the CPRD



Note: 'Healthier agers' were defined as non-smokers, without recent cancer (within the five previous years except non-melanoma skin cancer), dementia, heart failure, or multi-morbidity and survived the first 3.9 years of follow-up. Models were adjusted for gender, alcohol use, smoking history, calendar year, and socioeconomic status. The line in red is the hazard ratio and the broken lines in yellow are the 95% confidence intervals.

5.5.3. BMI categorical associations with mortality

For the two youngest age groups, the BMI range 23.0-26.9 kg/m^2 corresponded to the lowest mortality risk. This BMI range was used as the revised BMI referent group for the categorical associations. This was used for all age groups to enable comparisons between the magnitudes of the mortality risks for all the BMI groups. Following this revision, the other BMI (kg/m^2) groups were <18.5, 18.5-22.9, 27.0-29.9, 30.0-34.9, 35.0-39.9, and ≥40.0. For the distribution of outcomes see supplementary material Table S5.6 and S5.7. **Table 5.2** shows the BMI and mortality associations. In the 65 to 69 years age group those within the BMI 30.0-34.9 kg/m^2 (Obese-1) range had substantially raised mortality risks (HR 1.25 CI 1.19, 1.32) relative to those within the BMI 23.0-26.9 kg/m^2 range. Mortality risks for those within the BMI 30.0-34.9 kg/m^2 (Obese-1) range were raised in all age groups except those aged ≥85 years, for whom mortality risks were non-significant. Mortality risks for those within the BMI 35.0-39.9 kg/m^2 (Obese-2) and BMI ≥40.0 kg/m^2 (Obese-3) ranges were higher than those for the BMI Obese-1 range up to age 84 years; in the 65 to 69 years age group mortality hazards were 1.50 (CI 1.39, 1.62) and 2.35 (CI 2.13, 2.59) respectively. For those aged ≥85 years the mortality risks were non-significant for those with the BMI ≥35.0 kg/m^2 (Obese-2 and Obese-3) range relative to those within the BMI 23.0-26.9 kg/m^2 range. In the 65 to 69 years age group those within the BMI 27.0-29.9 kg/m^2 range had modestly raised mortality risks (HR 1.06 CI 1.01, 1.12). For those within the BMI 27.0-29.9 kg/m^2 range, mortality risks were non-significant in the 70 to 84 age range and paradoxical for those aged ≥85 years (HR 0.92 CI 0.87, 0.98). Mortality hazards were also raised for those within the BMI <18.5 kg/m^2 range relative to those within the BMI 23.0-26.9 kg/m^2 range in all age groups. For all age groups there was an increased mortality risk for those within the BMI 18.5-22.9 kg/m^2 range relative to those within the BMI 23.0-26.9 kg/m^2 range.

Table 5.2 | Hazard ratios for mortality by BMI category for 'healthier agers' by age group using the CPRD

	Age group (years)				
	60 to 64 [a]	**65 to 69** [a]	**70 to 74** [a]	**75 to 84** [a]	**≥85** [a]
BMI <18.5	69/767 2.35 (1.85, 2.99)	124/744 2.32 (1.94, 2.78	284/958 2.09 (1.86, 2.36)	940/1728 1.80 (1.68, 1.92)	581/791 1.53 (1.40, 1.67)
BMI 18.5-22.9	739/14777 1.18 (1.08, 1.28)	1274/12950 1.16 (1.09, 1.23)	2363/12402 1.19 (1.130, 1.25)	7275/17574 1.20 (1.16, 1.23)	3303/5266 1.15 (1.10, 1.20)
BMI 23.0-26.9	2064/41631 1.00	3627/37680 1.00	5868/34273 1.00	12898/36247 1.00	4143/7141 1.00
BMI 27.0-29.9	1686/29399 1.14 (1.07,1.21)	2750/26452 1.06 (1.01, 1.12)	3935/22655 1.02 (0.98, 1.06)	6963/20781 0.99 (0.96, 1.02)	1659/3066 0.92 (0.87, 0.98)
BMI 30.0-34.9	1714/26177 1.32 (1.24, 1.41)	2602/22475 1.25 (1.19 to 1.32)	3351/18118 1.16 (1.11, 1.21)	4842/14379 1.08 (1.04, 1.11)	915/1758 0.98 (0.91, 1.05)
BMI 35.0-39.9	691/8601 1.79 (1.64, 1.96)	844/6685 1.50 (1.39, 1.62)	11035/5031 1.46 (1.37, 1.57)	1176/3379 1.28 (1.20, 1.36)	188/319 1.00 (0.87, 1.16)
BMI ≥40.0	400/3608 2.65 (2.38, 2.96)	463/2574 2.35 (2.13, 2.59)	381/1564 1.98 (1.79, 2.20)	343/869 1.75 (1.57, 1.95)	

[a] Cell contents: events/number, HR (95% CI)

Note: 'Healthier agers' were non-smokers without recent cancer (within the previous five years excluding non-melanoma skin cancer), dementia, heart failure, or multi-morbidity and survived the first 3.9 years. Cox proportional hazards models were adjusted for age, gender, alcohol use, smoking, calendar year, and socioeconomic status. For the age ≥85 years age group the BMI Obese-2 and BMI Obese-3 were combined.

5.5.4. Absolute rates

For those aged 65 to 69 years at baseline with mean values for confounders, the estimated death rate between 4 to 14.9 years for those within the BMI 30.0-34.9 kg/m^2 (Obese-1) range was 27.9% (32.6% for BMI 35.0-39.9 kg/m^2 and 45.2% for BMI ≥40.0 kg/m^2), compared to 23.1% for those within the BMI 23.0-26.9 kg/m^2 range (**Table 5.3**). The estimated death rate during the first 3.9 years of follow-up for those aged 65 to 69 years was 3.0% for those within the BMI 30.0-34.9 kg/m^2 (Obese-1) range (3.6% for BMI 35.0-39.9 kg/m^2 and 4.7% for BMI ≥40.0 kg/m^2), compared to 2.7% for those within the BMI 23.0-26.9 kg/m^2 range.

Table 5.3 | Death Rates for the 'healthier agers' by BMI category for those aged 65 to 69 years at baseline using the CPRD

BMI category	0 to 3.9 years [a]	≥4 years [a]
BMI <18.5	11.1	49.5
BMI 18.5-22.9	3.8	27.0
BMI 23.0-26.9	2.7	23.1
BMI 27.0-29.9	2.6	24.3
BMI 30.0-34.9	3.0	27.9
BMI 35.0-39.9	3.6	32.6
BMI ≥40.0	4.7	45.2

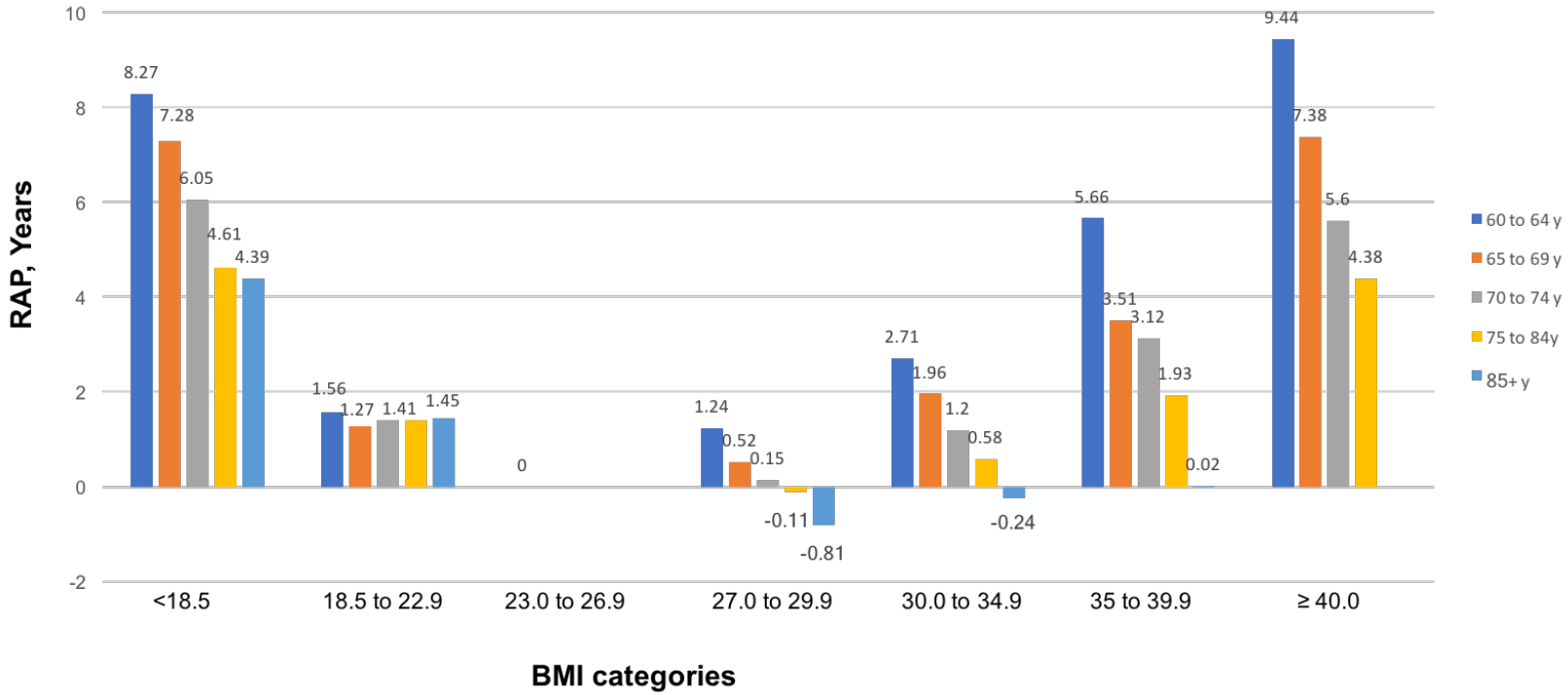
[a] Cell contents death %

Note: 'Healthier agers' were defined as non-smokers, without recent cancer (within the five previous years except non-melanoma skin cancer), dementia, heart failure, or multi-morbidity. Cox proportional hazards models were adjusted for age, gender, alcohol status, smoking status, calendar year, and Index Multiple of Deprivation.

5.5.5. Rate advancement period

Applying the rate advancement period approach to 'healthier agers' aged 65 to 69 years at baseline who are within the BMI 30.0-34.9 kg/m^2 (Obese-1), 35.0-39.9 kg/m^2 (Obese-2) and ≥40.0 kg/m^2 (Obese-3) ranges show longer term mortality rates, which is equivalent to being 1.96, 3.51 and 7.38 years older than their chronological age, respectively, compared to those within the BMI 23.0-26.9 kg/m^2 range (**Figure 5.6**). Age acceleration in the BMI 27.0-29.9 range was 0.52 years for those aged 65 to 69 years compared to those within the BMI 23.0-26.9 kg/m^2. Age accelerations were apparent for all age groups, except for those aged ≥85 years for the BMI 30.0-344.9 kg/m^2 (Obese-1) range, with an attenuation of the acceleration with advancing age. Age accelerations were observed for all age groups for the BMI <18.5 kg/m^2, BMI 18.5-22.9 kg/m^2, BMI 35.0-39.9 kg/m^2, and BMI ≥40.0 kg/m^2 ranges.

Figure 5.6 | Effective age estimates from the reported mortality hazard ratios for 'healthier agers' using the CPRD by age group



Note: 'Healthier agers' were defined as non-smokers, without recent cancer (within the five previous years except non-melanoma skin cancer), dementia, heart failure, or multi-morbidity and survived the first 3.9 years of follow-up. RAP: Rate advancement period.

5.5.6. Type 2 diabetes

For the distribution of outcomes see supplementary material Table S5.6 and S5.7. For 'healthier agers' the risk for incident diabetes was raised for the following ranges relative to those within the BMI 23.0-26.9 kg/m^2 for all age groups: BMI 27.0-29.9 kg/m^{2,} BMI 30.0-34.9 kg/m^2 (Obese-1), BMI 35.0-39.9 kg/m^2 (Obese-2), and BMI ≥40.0 kg/m^2 (Obese-3) (**Table 5.4**). The risks for diabetes for those within the BMI 27.0-29.9 kg/m^2 range was Sub-Hazard Ratio (SHR) 1.79 (CI 1.67, 1.93) and for those within the BMI 30.0-34.9 kg/m^2 (Obese-1) range it was SHR 2.68 (CI 2.49, 2.88) relative to those within the BMI 23.0-26.9 kg/m^2 range for those aged 65 to 69 years at baseline. Risks were reduced for those with BMI values <23.0kg/m^2 for those aged <85 years.

Table 5.4 | Competing sub-hazard ratios for incident type 2 diabetes for 'healthier agers' by age-group using a re-defined BMI referent group using the CPRD

	Age group (years)				
	60 to 64 [a]	**65 to 69** [a]	**70 to 74** [a]	**75 to 84** [a]	**≥85** [a]
BMI <18.5	4/740 0.19 (0.07, 0.51)	7/704 0.27 (0.13, 0.56)	13/898 0.32 (0.18, 0.55)	31/1645 0.45 (0.32, 0.64)	14/744 0.68 (0.39,1.18)
BMI 18.5-22.9	205/14027 0.50 (0.44, 0.59)	260/12001 0.56 (0.49, 0.64)	306/11250 0.61 (0.54, 0.69)	440/15985 0.65 (0.58, 0.72)	102/4764 0.77 (0.60, 0.98)
BMI 23.0-26.9	1192/37867 1.00	1345/33115 1.00	1321/29272 1.00	1318/31102 1.00	168/6110 1.00
BMI 27.0-29.9	1422/25031 1.83 (1.70, 1.98)	1552/21660 1.79 (1.67, 1.93)	1236/17989 1.55 (1.43, 1.67)	1013/16774 1.48 (1.36, 1.60)	102/2477 1.53 (1.20, 1.97)
BMI 30.0-34.9	1854/20534 3.05 (2.83, 3.28)	1718/16938 2.68 (2.49, 2.88)	1206/13163 2.16 (2.00, 2.34)	831/10783 1.98 (1.81, 2.16)	48/1343 1.41 (1.02, 1.95)
BMI 35.0-39.9	726/6089 4.43 (4.04, 4.87)	576/4487 3.66 (3.32, 4.05)	411/3325 3.18 (2.84, 3.56)	217/2250 2.55 (2.20, 2.94)	22/222 3.88 (2.47, 6.08)
BMI ≥40.0	328/2282 5.59 (4.92, 6.34)	241/1544 4.68 (4.07, 5.38)	111/916 3.18 (2.61, 3.87)	45/548 2.19 (1.62, 2.95)	

[a] Cell contents: events/number, HR (95% CI)

Note: 'Healthier agers' were non-smokers without recent cancer (within the previous five years excluding non-melanoma skin cancer), dementia, heart failure, or multi-morbidity and survived the first 3.9 years. Cox proportional hazards models were adjusted for age, gender, alcohol use, smoking, calendar year, and socioeconomic status. For the age ≥85 years age group the BMI Obese-2 and BMI Obese-3 were combined. Those with prevalent type 2 diabetes were excluded.

5.5.7. Coronary Heart Disease

For the distribution of outcomes see supplementary material Table S5.6 and S5.7. For CHD, competing hazards were raised for those within the BMI 27.0-29.9 kg/m^2 range in all age groups. Those within the BMI 30.0-34.9 kg/m^2 (Obese-1) range have raised risks for CHD to age 84 years and a non-significant CHD risk estimate in the ≥85 years age group relative to those within the BMI 23.0-26.9 kg/m^2 range (**Table 5.5**). The risks for CHD for those within the BMI 27.0-29.9 kg/m^2 was SHR 1.14 (CI 1.07, 1.22) and for those within the BMI 30.0-34.9 kg/m^2 (Obese-1) range it was SHR 1.26 (CI 1.17, 1.35) relative to those within the BMI 23.0-26.9 kg/m^2 range for those aged 65 to 69 years at baseline. The magnitudes for the risks of CHD for the higher BMI groups were less than those reported for incident diabetes.

Table 5.5 | Competing sub-hazard ratios for incident coronary heart disease for 'healthier agers' by age-group using a re-defined BMI referent group using the CPRD

	Age group (years)				
	60 to 64 [a]	**65 to 69** [a]	**70 to 74** [a]	**75 to 84** [a]	**≥85** [a]
BMI <18.5	14/745 0.65 (0.38, 1.09)	31/708 0.96 (0.68, 1.37)	50/892 0.85 (0.64, 1.12)	114/1604 0.79 (0.65, 0.95)	35/715 0.60 (0.43, 0.85)
BMI 18.5-22.9	341/14255 0.79 (0.70, 0.89)	489/12193 0.84 (0.76, 0.93)	682/11342 0.91 (0.83, 0.99)	1274/15753 0.89 (0.83, 0.95)	362/4645 0.97 (0.85, 1.11)
BMI 23.0-26.9	1377/39260 1.00	1833/34545 1.00	2139/30561 1.00	2916/31781 1.00	491/6136 1.00
BMI 27.0-29.9	1132/27284 1.16 (1.07, 1.26)	1468/23844 1.14 (1.07, 1.22)	1543/19847 1.12 (1.05, 1.19)	1753/18062 1.10 (1.03, 1.16)	248/2608 1.22 (1.05, 1.42)
BMI 30.0-34.9	1054/24179 1.25 (1.15, 1.36)	1296/20119 1.26 (1.17, 1.35)	1256/15854 1.19 (1.11, 1.28)	1168/12441 1.11 (1.04, 1.19)	111/1463 1.03 (0.84, 1.26)
BMI 35.0-39.9	366/7966 1.44 (1.28, 1.62)	377/6051 1.30 (1.16, 1.45)	321/4446 1.17 (1.04, 1.32)	262/2987 1.10 (0.97, 1.25)	25/278 1.12 (0.74, 1.67)
BMI ≥40.0	152/3333 1.49 (1.26, 1.77)	130/2318 1.21 (1.02, 1.45)	78/1389 0.97 (0.77, 1.21)	70/771 1.22 (0.97, 1.55)	

[a] Cell contents: events/number, HR (95% CI)

Note: 'Healthier agers' were non-smokers without recent cancer (within the previous five years excluding non-melanoma skin cancer), dementia, heart failure, or multi-morbidity and survived the first 3.9 years. Cox proportional hazards models were adjusted for age, gender, alcohol use, smoking, calendar year, and socioeconomic status. For the age ≥85 years age group the BMI Obese-2 and BMI Obese-3 were combined. Those with prevalent coronary heart disease were excluded.

5.5.8. Sensitivity analyses

Interactions between the BMI categories and gender were assessed for the 'healthier agers' which were not significant except in the 70 to 74 age-group (p=0.0447) where absolute differences in estimates were small, and there was overlap between the confidence intervals. Adjusting for physical activity level (**Table 5.6**) where available had little effect on mortality estimates. Restricting estimates to those with a 'white' ethnicity health record (**Table 5.7**) had little impact on estimates. Restricting mortality estimates to those with measured weight change (**Table 5.8**) were again little changed. In the ≥85 years age group, mortality risks were not significantly different for the BMI 27.0-29.9 kg/m^2 or BMI 30.0-34.9 kg/m^2 (Obese-1) ranges relative to those within the BMI range 23.0-26.9 kg/m^2. A similar model excluding measured weight losses of ≥2.5 kg also yielded similar estimates (**Table 5.9**). To check the robustness of estimates including unrecorded categories for smoking and alcohol use, mortality hazards with multiple imputation were estimated: results were little changed (**Table 5.10**). For the main analysis in this chapter the referent range was revised to include the BMI values 23.0 to <27.0 kg/m^2 as this range seemed to be associated with the lowest mortality risk in the two youngest groups. However, inclusion of the higher end of BMI Normal range (23.0 to <25.0 kg/m^2) and the lower end of the BMI Overweight range (25.0 to <27.0 kg/m^2) as one referent range challenges the interpretation of the mortality risks for those with a BMI in the Overweight range. In the modelling of the BMI continuous associations with mortality the risk appears similar for the higher end of the BMI Normal range and lower end of the BMI Overweight range for those aged <84 years, and appears a reduced risk for the higher BMI values for those aged ≥85 years. The analyses were, therefore, repeated using the higher BMI Normal range as the referent group (see supplementary material tables S5.8 to S5.17).

Mortality

For those aged <85 years the risks for mortality were not significantly different for those within the BMI range 25.0 to <27.0 kg/m^2 relative to those within the BMI range 23.0 to <25.0 kg/m^2, in all the analyses except the multiple imputation analysis for those aged 70 to 74 years with a reduced risk. Reduced risks were found for those aged ≥85 years in the main analysis, in the restriction to a 'white'

ethnicity record, exclusion of ≥2.5kg weight loss and multiple imputation, with the rest of the analyses being non-significant. Mortality risks were similar for all the BMI ranges to those reported when using the referent range 23.0 to <27.0 kg/m^2. Except, there were shifts to non-significance in the BMI range 27.0 to <30.0 kg/m^2 (60 to 64 age-group: exclusion ≥2.5kg weight loss; 65 to 69 years: restriction to a 'white ethnicity record, exclusion ≥5.0kg weight loss, and multiple imputation) and reduced risks (age group 70 to 74 years after restricting to a 'white' ethnicity record; ≥85 years multiple imputation) The BMI Obese-1 mortality risks for those aged 75 to 84 years also became not significantly different to those within the range 23.0 to <25.0 kg/m^2 after the exclusions of ≥5.0kg weight loss. For those aged ≥85 years, mortality risks for the BMI range 18.5 to 22.9 kg/m^2 became not significantly different to those within the referent range 23.0 to <25.0 kg/m^2 after the exclusion of ≥5.0kg weight loss and ≥2.5kg weight loss. Reduced risks were also reported for the BMI Obese-1 range for multiple imputation for those aged ≥85 years.

Coronary heart disease

For the coronary heart disease analyses, the risks were little changed. There was no significant difference between the BMI range 25.0 to <27.0 kg/m^2 compared to those within the BMI range 23.0 to <25.0 kg/m^2, except for those aged 65 to 69 where there was a 12% increased risk (95% CI 1.02, 1.23).

Diabetes

For the diabetes analyses, the point estimates for the higher BMI values were greater. For the two youngest age-groups, the point estimates and confidence intervals were above those reported. There were increased risks for those within the BMI range 25.0 to <27.0 kg/m^2 compared to the referent range 23.0 to <25.0 kg/m^2, for those aged <85 years.

Table 5.6 | Hazard ratios (95% CI) for mortality by BMI category and age-group for 'healthier agers' with the inclusion of an activity variable.

	Age group (years)				
	60 to 64 [a]	**65 to 69** [a]	**70 to 74** [a]	**75 to 84** [a]	**≥85** [a]
BMI <18.5	38/410	53/365	124/487	472/882	297/410
	2.68 (1.94, 3.71)	2.10 (1.59, 2.77)	1.82 (1.52, 2.19)	1.92 (1.75, 2.11)	1.64 (1.46, 1.86)
BMI 18.5-22.9	383/8286	692/7349	1267/6866	3840/9553	1773/2916
	1.15 (1.02, 1.29)	1.22 (1.09, 1.36)	1.22 (1.15, 1.31)	1.20 (1.16, 1.25)	1.17 (1.10, 1.25)
BMI 23.0-26.9	1112/23592	2001/21467	3148/19509	6914/20541	2230/4024
	1.00	1.00	1.00	1.00	1.00
BMI 27.0-29.9	867/16334	1481/14798	2148/12932	3772/11712	896/1744
	1.10 (1.01, 1.21)	1.04 (0.97, 1.11)	1.03 (0.98, 1.09)	1.01 (0.97, 1.05)	0.90 (0.83, 0.97)
BMI 30.0-34.9	832/14071	1342/12110	1818/9980	2554/8025	475/970
	1.27 (1.16, 1.39)	1.25 (1.15, 1.35)	1.21 (1.14, 1.28)	1.06 (1.01, 1.11)	1.00 (0.90, 1.10)
BMI 35.0-39.9	325/4523	383/3465	517/2687	600/1834	105/182
	1.75 (1.54, 1.98)	1.39 (1.24, 1.57)	1.40 (1.28, 1.54)	1.24 (1.14, 1.35)	0.94 (0.77, 1.15)
BMI ≥40.0	191/1830	232/1325	194/860	171/479	
	2.77 (2.37, 3.24)	2.34 (2.03, 2.71)	1.96 (1.69, 2.27)	1.46 (1.25, 1.70)	

[a] Cell contents: events/number, HR (95% CI)

Note: 'Healthier agers' were non-smokers without recent cancer (within the previous five years excluding non-melanoma skin cancer), dementia, heart failure, or multi-morbidity and survived the first 3.9 years. Cox proportional hazards models were adjusted for age, gender, alcohol use, smoking, calendar year, physical activity, and socioeconomic status. For the age ≥85 years age group the BMI Obese-2 and BMI Obese-3 were combined.

Table 5.7 | Hazard ratios (95% CI) for mortality by BMI category and age-group for 'healthier agers' restricted to patients with a 'white' ethnicity record

	Age group (years)				
	60 to 64 [a]	**65 to 69** [a]	**70 to 74** [a]	**75 to 84** [a]	**≥85** [a]
BMI <18.5	60/580	102/581	246/765	821/1498	503/690
	2.47 (1.91, 3.20)	2.34 (1.92, 2.85)	2.18 (1.92, 2.48)	1.82 (1.69, 1.95)	1.55 (1.41, 1.70)
BMI 18.5-22.9	637/11207	1096/10353	2064/10297	6326/14988	2758/4483
	1.21 (1.11, 1.33)	1.17 (1.09, 1.26)	1.20 (1.14, 1.26)	1.20 (1.16, 1.24)	1.13 (1.07, 1.19)
BMI 23.0-26.9	1768/32416	3120/30598	5120/28762	11391/31480	3614/6257
	1.00	1.00	1.00	1.00	1.00
BMI 27.0-29.9	1442/23302	2418/21767	3480/19267	6150/18133	1450/2718
	1.12 (1.04, 1.20)	1.07 (1.01, 1.12)	1.01 (0.97, 1.06)	0.98 (0.95, 1.01)	0.93 (0.87, 0.98)
BMI 30.0-34.9	1472/20988	2280/18694	2985/15429	4324/12636	798/1531
	1.28 (1.20, 1.38)	1.24 (1.17, 1.31)	1.16 (1.11, 1.21)	1.07 (1.03, 1.11)	1.00 (0.92, 1.08)
BMI 35.0-39.9	600/7006	723/5588	920/4289	1024/2913	155/275
	1.74 (1.59, 1.91)	1.43 (1.32, 1.55)	1.46 (1.36, 1.57)	1.25 (1.17, 1.33)	0.94 (0.80, 1.11)
BMI ≥40.0	359/3040	418/2200	334/1328	290/754	
	2.59 (2.30, 2.90)	2.32 (2.09, 2.57)	1.97 (1.76, 2.20)	1.68 (1.50, 1.89)	

[a] Cell contents: events/number, HR (95% CI)

Note: 'Healthier agers' were non-smokers without recent cancer (within the previous five years excluding non-melanoma skin cancer), dementia, heart failure, or multi-morbidity and survived the first 3.9 years. Cox proportional hazards models were adjusted for age, gender, alcohol use, smoking, calendar year, and socioeconomic status. For the age ≥85 years age group the BMI Obese-2 and BMI Obese-3 were combined.

Table 5.8 | Hazard ratios (95% CI) for mortality by BMI category and age-group for 'healthier agers' with the exclusion of patients with measured weight loss ≥5kg in the weight stability subgroup.

	Age group (years)				
	60 to 64 [a]	**65 to 69** [a]	**70 to 74** [a]	**75 to 84** [a]	**≥85** [a]
BMI <18.5	24/260 2.72 (1.81, 4.08)	39/248 2.28 (1.66, 3.14)	92/337 2.12 (1.72, 2.62)	281/572 1.75 (1.55, 1.97)	185/289 1.48 (1.27, 1.72)
BMI 18.5-22.9	233/5349 1.13 (0.98, 1.31)	432/4908 1.14 (1.03, 1.27)	815/4857 1.15 (1.06, 1.25)	2370/6414 1.15 (1.10, 1.21)	1241/2264 1.11 (1.03, 1.19)
BMI 23.0-26.9	754/16239 1.00	1445/16022 1.00	2430/15603 1.00	5199/15997 1.00	1827/3549 1.00
BMI 27.0-29.9	769/13234 1.21 (1.09, 1.33)	1257/12674 1.08 (1.00, 1.16)	1814/11530 1.01 (0.95, 1.08)	3113/10128 1.01 (0.97, 1.06)	803/1645 0.94 (0.87, 1.03)
BMI 30.0-34.9	816/13259 1.30 (1.18, 1.44)	1298/11935 1.26 (1.17, 1.36)	1694/10062 1.14 (1.07, 1.21)	2253/7519 1.08 (1.03, 1.13)	465/986 1.03 (0.93, 1.14)
BMI 35.0-39.9	361/4905 1.72 (1.52, 1.95)	461/3996 1.44 (1.29, 1.60)	571/3005 1.45 (1.32, 1.59)	611/1947 1.35 (1.24, 1.46)	107/186 1.05 (0.86, 1.27
BMI ≥40.0	238/2267 2.71 (2.33, 3.14)	285/1626 2.44 (2.14, 2.77)	227/989 2.08 (1.81, 2.38)	181/515 1.74 (1.50, 2.02)	

[a] Cell contents: events/number, HR (95% CI)

Note: 'Healthier agers' were non-smokers without recent cancer (within the previous five years excluding non-melanoma skin cancer), dementia, heart failure, or multi-morbidity and survived the first 3.9 years. Cox proportional hazards models were adjusted for age, gender, alcohol use, smoking, calendar year, and socioeconomic status. For the age ≥85 years age group the BMI Obese-2 and BMI Obese-3 were combined.

Table 5.9 | Hazard ratios (95% CI) for mortality by BMI category and age-group for 'healthier agers' with the exclusion of patients with measured weight loss ≥2.5kg in the weight stability subgroup

	Age group (years)				
	60 to 64 [a]	**65 to 69** [a]	**70 to 74** [a]	**75 to 84** [a]	**≥85** [a]
BMI <18.5	21/202 3.14 (2.03, 4.86)	26/177 2.13 (1.44, 3.14)	67/240 2.22 (1.74, 2.83)	194/415 1.66 (1.43, 1.91)	120/188 1.48 (1.22, 1.78)
BMI 18.5-22.9	184/4444 1.12 (0.95, 1.33)	339/3973 1.15 (1.02, 1.30)	639/3924 1.16 (1.06, 1.27)	1838/5028 1.16 (1.10, 1.23)	945/1720 1.11 (1.02, 1.20)
BMI 23.0-26.9	635/14103 1.00	1195/13673 1.00	2011/13294 1.00	4340/13480 1.00	1481/2892 1.00
BMI 27.0-29.9	658/11768 1.18 (1.06, 1.32)	1114/11260 1.12 (1.04, 1.22)	1616/10239 1.04 (0.98, 1.11)	2695/8851 1.02 (0.98, 1.08)	682/1401 0.95 (0.87, 1.04)
BMI 30.0-34.9	719/11923 1.30 (1.17, 1.45)	1164/10806 1.30 (1.20, 1.41)	1515/9050 1.17 (1.09, 1.25)	2002/6709 1.10 (1.04, 1.16)	397/852 1.01 (0.90, 1.13)
BMI 35.0-39.9	323/4473 1.73 (1.51, 1.98)	407/3610 1.45 (1.30, 1.63)	520/2734 1.50 (1.36, 1.65)	535/1750 1.34 (1.22, 1.46)	96/164 1.09 (0.89, 1.35)
BMI ≥40.0	220/2103 2.79 (2.38, 3.26)	259/1504 2.49 (2.17, 2.85)	207/906 2.19 (1.89, 2.53)	171/475 1.83 (1.57, 2.14)	

[a] Cell contents: events/number, HR (95% CI)

Note: 'Healthier agers' were non-smokers without recent cancer (within the previous five years excluding non-melanoma skin cancer), dementia, heart failure, or multi-morbidity and survived the first 3.9 years. Cox proportional hazards models were adjusted for age, gender, alcohol use, smoking, calendar year, and socioeconomic status. For the age ≥85 years age group the BMI Obese-2 and BMI Obese-3 were combined.

Table 5.10 | Hazard ratios (95% CI) for mortality by BMI category and age-group for 'healthier agers' with multiple imputation of missing smoking and alcohol records

	Age group (years)				
	60 to 64 [a]	**65 to 69** [a]	**70 to 74** [a]	**75 to 84** [a]	**≥85** [a]
BMI <18.5	110/1017 2.81 (2.32, 3.40)	183/972 2.57 (2.22, 2.99)	372/1252 2.11 (1.90, 2.35)	1271/2354 1.82 (1.72, 1.93)	753/1049 1.55 (1.43, 1.67)
BMI 18.5-22.9	960/18030 1.23 (1.14, 1.33)	1591/15773 1.19 (1.12, 1.26)	2970/15350 1.22 (1.16, 1.27)	8992/21958 1.20 (1.17, 1.23)	4092/6516 1.16 (1.11, 1.21)
BMI 23.0-26.9	2495/49808 1.00	4343/45062 1.00	7030/41020 1.00	15708/44189 1.00	5064/8710 1.00
BMI 27.0-29.9	2033/35370 1.11 (1.05, 1.18)	3323/31770 1.06 (1.01, 1.11)	4768/27187 1.03 (0.99, 1.07)	8523/25328 0.99 (0.96, 1.02)	2035/3696 0.95 (0.90, 1.00)
BMI 30.0-34.9	2114/32161 1.30 (1.22, 1.38)	3199/27343 1.25 (1.19, 1.30)	4120/22126 1.16 (1.12, 1.20)	6044/17801 1.09 (1.05, 1.12)	1135/2138 1.00 (0.94, 1.06)
BMI 35.0-39.9	853/10704 1.73 (1.60, 1.87)	1071/8297 1.51 (1.41, 1.61)	1301/6210 1.46 (1.37, 1.55)	1483/4269 1.27 (1.20, 1.34)	248/411 1.03 (0.91, 1.17)
BMI ≥40.0	527/4635 2.65 (2.41, 2.91)	579/3253 2.29 (2.10, 2.50)	497/1998 1.99 (1.81, 2.18)	428/1092 1.69 (1.53, 1.86)	

[a] Cell contents: events/number, HR (95% CI)

Note: 'Healthier agers' were non-smokers without recent cancer (within the previous five years excluding non-melanoma skin cancer), dementia, heart failure, or multi-morbidity and survived the first 3.9 years. Cox proportional hazards models were adjusted for age, gender, alcohol use, smoking, calendar year, and socioeconomic status. For the age ≥85 years age group the BMI Obese-2 and BMI Obese-3 were combined.

5.6. Discussion

The aim of this chapter was to re-define the BMI referent range and to use this revised group to estimate the BMI associations with mortality, CHD, and diabetes. The results show that for 'healthier agers' (non-smokers, free of conditions associated with weight loss, and excluding early deaths) those within the BMI 30.0-34.9 kg/m^2 (Obese-1) range have elevated risks for all-cause mortality, coronary heart disease, and diabetes, compared to the risk nadir (23.0-26.9 kg/m^2) up to and including those aged 84 years. For 'healthier agers' these results do not support calls to revise policies to reflect the claimed obesity risk paradox in the general older population. At age 65 years, 'healthier agers' have long life expectancies (women 21.0 years, men 18.5 years for England) (Office for National Statistics, 2014) during which gains from optimised weight control could be enjoyed. My analysis showed that the evidence on being overweight at older ages is mixed, but BMI >27.0 kg/m^2 was associated with modestly increased mortality risks for the younger age groups (60 to 64 years; 65 to 69 years) relative to those within the BMI 23.0-26.9 kg/m^2 range. On the whole, the mortality risks for those within the lower end of the BMI Overweight range (BMI 25.0 to <27.0 kg/m^2) tended to be similar to those within the higher end of BMI Normal 23.0 to <25.0 kg/m^2 for those aged <85 years. Persons, within the BMI range 25.0 to <27.0 kg/m^2 did, however, have an increased risk of incident diabetes relative to those within the BMI range 23.0 to <25.0 kg/m^2.

Interestingly, even after excluding smokers and those with conditions associated with major weight loss (cancer, dementia, heart failure, and multi-morbidity) those within the lower end of the BMI Normal range (18.5 to <23.0 kg/m^2) had increased mortality risks compared to those with a BMI range of 23.0 to <25.0 or 23.0 to <27.0 kg/m^2. This is in-line with several previous analyses. Berrington de Gonzalez *et al*., (2010) reported that for never smokers, with at least one year of follow-up and without cancer or heart disease at baseline there was an increased mortality risk for those within the BMI range 18.5-19.9 kg/m^2 (aged 60 to 69 years HR 1.15 CI 1.04, 1.27; aged 70 to 84 years HR 1.32 CI 1.15, 1.51) relative to those with a BMI within the range 22.5-24.9 kg/m^2 with a median follow-up duration of 10 years using data from 19 pooled prospective cohort studies (Berrington de Gonzalez *et al.*, 2010). Similarly, increased mortality risks were

reported for those with BMI values <22.5 kg/m^2 relative to those with a BMI within the range 22.5 to <25.0 for never smoking adults 70 to 89 years, without prevalent chronic disease, and the first five years of follow up excluded (Di Angelantonio *et al.*, 2016). Conversely, Park *et al.*, (2012) showed that the mortality risks for those within the BMI range 18.5-22.9 kg/m^2 were not significantly different to those within the BMI range 23.0-24.9 kg/m^2 during a 12.5 year follow-up duration for adults aged 65 to 74 years after excluding smokers, those with cancer or heart disease, plus the first three years of follow up (Park *et al.*, 2012).

In the analysis presented in this chapter, the exclusion of conditions associated with weight loss did not capture all the patients with measured substantial weight loss thereby residual confounding may have remained in the models, which could partly explain the increased mortality risks for those within the lower end of the conventional BMI Normal range. Additionally, several diseases have a long pre-clinical weight loss stage, such as dementia (**Chapter 6**), which may not have been captured by excluding the first 3.9 years. Unmeasured confounders such as nutrition could have contributed to the risks. Furthermore, as highlighted previously BMI does not measure body compositional changes with ageing. Persons within the lower end of the BMI Normal range may conceivably be defined as having sarcopenia or be centrally obese. The causes of deaths also may differ for those within the BMI Normal range to those with higher BMI values e.g. higher risk from respiratory or other causes (i.e. not cancer or cardiovascular) (Pischon, et al., 2010).

My analysis showed that there were increased mortality risks for those with BMI values <23.0 kg/m^2. Inclusion of persons within the lower end of the BMI Normal range (<23.0 kg/m^2) as part of the referent group can distort mortality risk estimates for the higher BMI values. In comparison to the results presented in **Chapter 4**, where the whole of the conventional BMI Normal range was used as the referent group, the point estimates for the BMI Obese ranges were much higher when the BMI referent range commenced at 23.0 kg/m^2. Additionally, persons with the BMI Normal range may not be 'ideal' for other adiposity measures such as central adiposity or for body composition. This again may distort mortality risks. This will be examined further in **Chapter 8**.

5.6.1. Comparison to previous literature

The results from this chapter are difficult to compare with previous work due to the use of different age groups, exclusions, and the choice of the BMI referent group. The nadir of the mortality risk estimates is not easy to compare with prior analyses as none of the previous analyses reported estimates after sequential exclusion of smokers, those with conditions associated with weight loss, or deaths during the early stages of follow-up.

The results of this chapter for the BMI Overweight and BMI Obese-1 ranges are partly in accord with other analyses which excluded smokers, conditions associated with weight loss, and early deaths. Berrington de Gonzalez *et al* (2010) reported increased mortality risks for the upper end of the BMI Overweight (27.5-29.9 kg/m^2) and BMI Obese-1 ranges for two age groups, 60 to 69 years and 70 to 84 years, relative to those within the BMI 22.5-24.9 kg/m^2 range (Berrington de Gonzalez *et al.*, 2010). Park *et al.*, (2012) reported increased mortality risks for the BMI Obese-1 range relative to those within the BMI 23.0-24.9 kg/m^2 range for adults aged 65 to 74 years. There were increased mortality risks for males within the upper end of the BMI Overweight range (27.5-29.9 kg/m^2), and a non-significant mortality risk for females relative to those within the BMI referent group (Park *et al.*, 2012).

The results presented within this chapter for incident type 2 diabetes and coronary heart disease are also difficult to compare to previous analyses. Overall, the results from this chapter showed an increased risk for type 2 diabetes for the BMI Overweight and BMI Obese ranges which parallels those reported in the supplementary material table S5.2. The attenuation of the risks for incident type 2 diabetes with advancing age are similar to those that were reported by Biggs *et al.*, (2010) (Biggs *et al.*, 2010). However, limited studies used a competing risk approach and there were no studies providing diabetes risk estimates across narrower age groups using a baseline period within the 21st century. Likewise, very few studies as shown in supplementary material table S5.4 used the competing risk technique for CHD and there were no studies reporting estimates for progressively older age groups using a baseline period within the 21st century.

5.6.2. Strengths and limitations

In this chapter I re-defined the BMI referent group by estimating the continuous BMI association with mortality. A major criticism of the meta-analysis by Flegal *et al.*, (2013) was the use of the conventional BMI Normal range (Flegal *et al.*, 2013). The results presented in this chapter provide further evidence that participants within the lower BMI Normal range may be at an elevated mortality risk which can distort mortality risk estimates for higher BMI categories. As noted in **Chapter 4** a major strength of the sequential exclusions leading to the 'healthier agers' subgroup was that the sample sizes for the age groups are much greater than previous analyses (**Chapter 3**). In this chapter I report recent estimates for incident CHD and incident diabetes across progressively older age groups using a competing risks approach adding to the limited evidence in this research area. Another advantage to this analysis is that outcome ascertainment is improved using both health records from general practitioner visits and hospital admissions.

There are several limitations for this analysis. In this analysis, I estimated the association with BMI and all-cause mortality, CHD, and type 2 diabetes, it is also important to establish associations with other health outcomes which are of relevance in later life. The risk estimates reported in this chapter may differ when other health outcomes are considered. As highlighted in **Chapter 4** the patients were predominately 'white' ethnicity and, therefore, the findings may not be generally applicable to other ethnic groups. These results also are derived from a group of 'healthier agers'. This group of patients would be the main target for obesity prevention. As highlighted in this chapter, the nadir of the mortality risk curves was slightly higher at older ages. A decision was made to use the mortality risk nadir from the two youngest age groups. This allowed direct comparisons between the differing age groups. An extension of this work would be to increase the BMI values within the BMI referent group for these older age groups.

In **Chapter 6** I use the CPRD database to estimate the association between BMI categories with incident dementia for those aged 65 to 74 years. Risks for dementia have also been reported to be paradoxical in later life with higher BMI categories. Increased risks for incident dementia for the BMI Obese range have been reported for younger and middle aged cohorts relative to those within the

BMI Normal range. Reduced, non-signifcant, and increased risks for dementia have been reported for older adults relative to those within the BMI Normal range (**Chapter 6**).

Future work is required to establish whether other measures of adiposity or body composition may improve mortality prediction compared to BMI. As highlighted in **Chapter 1**, the value of BMI as a surrogate adiposity measure for older age groups has been questioned due to the alteration of body composition and fat distribution across the life cycle. In **Chapter 7** I use the UK Biobank to compare established measures of body fat distribution (waist circumference, waist-to-hip ratio, and waist-to-height ratio) and body composition (percentage body fat, fat mass, fat free mass, and skeletal mass index) to BMI in their ability to predict mortality for 'healthier agers' within the seventh decade of life.

5.7. Conclusions

The use of the conventional BMI Normal range (18.5 to <25.0 kg/m^2) appears too broad for defining those with Normal BMI in later life. Persons with BMI values below <23.0 kg/m^2 have increased mortality risks, and the inclusion of this group in the BMI referent group can distort mortality risks for higher BMI values. In this large population-based older cohort studying longer-term outcomes, the results show that obesity is associated with shorter survival in older people who do not have the studied confounding factors, at least to and including those aged 84 years. These results cast doubt on calls to revise obesity control policies to reflect the claimed obesity risk paradox in the general older population. The implications of these findings will be discussed in greater detail in **Chapter 9**.

Supplementary material for Chapter 5

List of Tables for supplementary material Chapter 5

Table S5.1 | Reported associations using Odds Ratios between BMI and coronary heart disease/ MI for adults aged ≥65 years and ≥1000 subjects

Study; baseline year(s) (Author, year)	Subjects	Follow-up; [events]	Model adjustments	BMI groups [methods]	Results
5 states- Arizona, California, Colorado, New Mexico, & Texas of the Hispanic Established Population for the Epidemiological Study of the Elderly 1993–94 (Otiniano *et al.*, 2003)	*n* = 2,772 without heart attack at baseline 65 – 107y	7 y (follow-ups in 1995-96, 1998–99, and 2000–01) [self-report heart attack; first follow up 139; first to second 170 – sample size 2,122 – second to third follow up 121 – sample size 1,679]	Age, sex, education, living arrangement, smoking, diabetes, hypertension, & stroke	ref BMI <30 first follow-up ≥30.0 second follow-up ≥ 30.0 third follow-up ≥30.0 [not reported]	 0.96 (0.66, 1.41) 1.26 (0.90, 1.75) 1.38 (0.94, 2.04)
5 states- Arizona, California, Colorado, New Mexico, & Texas of the Hispanic Established Population for the Epidemiological Study of the Elderly 1993–94 (Otiniano *et al.*, 2005)	*n* = 2,772 without heart attack at baseline 65 – 107y	7 y (max)	Metabolic syndrome, age, gender, living alone, y of education, current smoking, current drinking, any ADL limitation, DM only, & hypertension only	<30.0 ≥30.0 [not reported]	1.00 2.49 (1.30, 4.79)

Table S5.2 | Reported associations using Hazard Ratios or Relative Risks between BMI and coronary heart disease/MI for adults ≥65 years and ≥1000 subjects

Study; baseline year(s) (Author, year)	Subjects	Follow-up; [events]	Model adjustments	BMI groups [methods]	Results
Nord-Trøndelag Health Study (Norway) 1984-1986 (Ellekjaer, Holmen and Vatten, 2001)	3,034 M with BMI 3,123 F with BMI ≥70 y Excluded those with stroke, CHD, DM and using blood pressure medication	9.1 (median) [365 M & 242 F]	Age, systolic BP categories, & current smoking	M ≤22.95 22.96-25.10 25.11-27.35 ≥21.36 p for trend F ≤23.23 23.24-25.97 25.98-29.00 ≥29.01 p for trend [Measured]	 1.00 0.80 (0.58, 1.11) 0.98 (0.71, 1.34) 0.99 (0.71, 1.36) p = 0.76 1.00 0.97 (0.65, 1.45) 0.99 (0.67, 1.48) 0.81 (0.86, 2.52) p = 0.35
CHS 1989-1990 (Janssen, 2007)	*n* = 4,968 ≥65y excluded institutionalized, required proxy respondent & BMI <18.5	Age, sex, race, SES, smoking, PA, & previous CHD events	9 y (max) [586 MI cases]	20.0-24.9 25.0-29.9 ≥30.0 [Measured]	1.00 1.16 (0.96, 1.39) 1.16 (0.91, 1.47)

Table S5.2 continued

Study; baseline year(s) (Author, year)	Subjects	Follow-up; [events]	Model adjustments	BMI groups [methods]	Results
CHS 1989-1990; 1992-1993 (Kizer *et al.*, 2011)	*n* = 3,754 excluded individuals with prevalent CVD (CHD, stroke, TIA, PAD, HF) and atrial fibrillation 65 - 100 y	14 y (median) [nonfatal MI and fatal coronary events 845]	Age, sex, race, smoking status, PA, alcoholic drinks/week, educational attainment, serum creatinine, & HRT (women)	<25.0 25.0-29.9 30.0-34.9 ≥35.0 p for trend [Measured]	1.00 1.03 (0.90, 1.20) 1.42 (1.16, 1.73) 1.70 (1.23, 2.35) <0.001
The Uppsala Longitudinal Study of Adult Men (ULSAM), 1991–1995 (Möller *et al.*, 2006)	1,221 M ≥70 y	10.4 y (max) [84 MI]	Univariate	BMI per 1 SD increase [Not reported]	1.17 (0.96, 1.44)

Table S5.2 continued

Study; baseline year(s) (Author, year)	Subjects	Follow-up; [events]	Model adjustments	BMI groups [methods]	Results
Health, Aging and Body Composition Study April 1997-June1998 (Nicklas *et al.*, 2004)	1,116 M & 1,387 F 70 to 79 y eligible for the study if they reported no difficulty walking a quarter mile, climbing 10 steps, or performing basic ADLS. Excluded those with a life-threatening illness, had a history of active cancer in the 3 y prior, did not plan to remain in the geographic area for at least 3 y, or were participating in another research study involving modification of their eating or exercise behavior.	4.6 y (mean; SD 0.9) [death from MI or any overnight hospitalization for MI 71 M and 45 F]	Age, race, education, smoking, COPRD, & HRT (women)	per 4.9 kg/m^2 increase [Measured]	M 1.00 (0.75, 1.35) F 1.15 (0.88 ,1.51)

Table S5.2 continued

Study; baseline year(s) (Author, year)	Subjects	Follow-up; [events]	Model adjustments	BMI groups [methods]	Results
Pooled analysis of 51 studies (Wormser *et al.*, 2011)	203,338 participants overall ≥70y	5.7 y (median overall) [3,049 CHD]	Age, smoking, sex	Per 4.56 kg/m^2 higher BMI from 20	1.12 (1.05, 1.19)

Table S5.3 | Reported associations using Odds Ratios between BMI and diabetes for adults aged ≥65 years and ≥1000 subjects

Study; Baseline year(s) (Author, year)	**Subjects**	**Follow up; [events]**	**Model adjustments**	**BMI groups [method]**	**Results**
Australian Women's Health Survey 1996 (Strodl and Kenardy, 2006)	*n* = 8,896 F 70 - 74 years	3 y (max) [243]	Number of visits to GP, hypertension, mental health index, & education	18.5 - <25.0 25.0 - <30.0 ≥ 30.0 [Self-report -with an algorithm]	1.00 1.62 (1.16, 2.28) 2.79 (1.93, 4.03)

Table S5.4 | Reported associations using Hazard Ratios between BMI and diabetes for adults aged ≥65 years and ≥1000 subjects

Study; Baseline year(s) (Author, year)	Subjects	Follow up; [events]	Model adjustments	BMI groups [method]	Results
Cardiovascular Health Study 1989-1990;1992; 1993 (Biggs *et al.*, 2010)	1,736 M & 2,457 F ≥65 y	17.8y (max) [149 M & 190 F]	Age, race, current smoking, PA, diet score, & alcohol consumption	Males	
				<23.3	1.00
				23.3 - 25.0	1.9 (0.9, 4.3)
				25.1 - 26.6	2.9 (1.3, 6.1)
				26.7 - 28.6	4.4 (2.1, 9.1)
				≥28.7	5.6 (2.7, 11.4)
				per SD increase	1.7 (1.4, 2.0)
				Females	
				<22.2	1.00
				22.2 - 24.4	0.9 (0.5, 1.6)
				24.5 - 26.6	1.4 (0.8, 2.5)
				26.7 - 29.6	1.6 (0.9, 2.7)
				≥29.7	3.7 (2.3, 6.2)
				per SD increase	1.5 (1.4, 1.7)
				65 to <75 y*	
				1	1.00
				2	1.6 (1.1, 2.4)
				3	4.0 (2.8, 5.7)
				≥75 y*	
				1	1.00
				2	2.0 (1.1, 3.6)
				3	1.9 (1.0, 3.6)
				[Measured]	

Table S5.4 continued

Study; Baseline year(s) (Author, year)	Subjects	Follow up; [events]	Model adjustments	BMI groups [method]	Results
City of Hefei, urban china 2001 (Chen *et al.*, 2012)	*n* = 1,317 65 - 99y	7.5y [119]	Age, annual income, smoking habits, walking, marital status, living with, frequency of visiting children or other relatives, GMS-AGECAT syndrome level, hypochondriasis, hypertension, hypercholesterolemia, hearing problems, & activities	<18.5 18.5 - 23.9 24.0 - 27.9 ≥28.0 [Measured]	0.63 (0.22, 1.82) 1.00 1.81 (1.19, 2.76) 1.77 (0.97, 3.25)
Chiba City 1994 Kashiwa City 2002 (Fujita, Ueno and Hata, 2009)	Chibia city 1,787 M 2,643 F Kashiwa city 2,748 M 3,785 F 70 - 79 y	Chiba city up to 2005 9.8 y (median) for M & 10.3 (median) for F [236 M & 279 F] Kashiwaa cohort up to 2006 4.0 y (median) for M & 4.0 y (median) for F [282 M & 230 F]	Chiba cohort: smoking habit, FH DM, alcohol consumption & glucose type Kashiwa: current smoking habit, FH DM, fasting blood glucose & HbA_{1c}	Ref 18.5 - <25.0 Chiba cohort M <18.5 ≥25.0 F <18.5 ≥25.0 Kashiwa cohort M <18.5 ≥25.0 Women <18.5 ≥25.0 [Measured]	1.00 1.18 (0.71, 1.95) 1.79 (1.35, 2.39) 0.75 (0.46, 1.21) 1.40 (1.08, 1.80) 1.67 (1.02, 2.71) 1.33 (1.03, 1.73) 1.86 (1.20, 2.89) 1.17 (0.89,1.53)

Table S5.4 continued

Study; Baseline year(s) (Author, year)	**Subjects**	**Follow up; [events]**	**Model adjustments**	**BMI groups [method]**	**Results**
CHS 1989-1990; 1992-1993 (Imamura *et al.*, 2013)	*n* = 3,899 (no diabetes at baseline and alive after one year) 65 - 98 y	11.7 y (median) [274]	Sex, age, race, BP >130/85 / hypertension medication, HDL-C, triglyceride level, fasting glucose	<25.0 25.0 - 29.9 ≥30.0	1.00 1.18 (0.88, 1.58) 1.83 (1.32, 2.54)
CHS (limited access dataset) June 1989 and June 1990, (Janssen, 2007)	*n* = 3,381 ≥65 y excluded <18.5	9 y [211]	Age, sex, race, SEX, smoking, & PA	20.0 - 24.9 25.0 - 29.9 ≥30.0 [Measured]	1.00 1.78 (1.24, 2.57) 4.15 (2.82, 6.12)
CHS 1989-1990; 1992 (Mozaffarian *et al.*, 2009)	*n* = 4,883 65 - 98 y	10 y Diabetes (337)	Age, sex, race, educational level, & annual income	<25.0 ≥25.0 [measured]	0.38 (0.29, 0.51) 1.00

Table S5.4 continued

Study; Baseline year(s) (Author, year)	Subjects	Follow up; [events]	Model adjustments	BMI groups [method]	Results
Singapore Chinese Health Study April 1993-December 1998 Odegaard *et al.*, 2009)	*n* = 4,817 no DM, cancer, heart disease, or stroke ≥65 y	follow up interviews 1999 and 2004 [nr]	Age, sex, ethnicity, y of interview, hypertension, smoking history, education, alcohol intake, dietary factors, & moderate & strenuous PA in hours per week	<18.5 18.5 - 23 23.0- 27.5 >27.5 [Self-report]	1.00 2.0 (1.0, 4.2) 3.3 (1.6, 6.9) 7.0 (3.3, 14.8)
Prospective Study of Pravastatin in the Elderly at Risk (PROSPER) Dec 15 1997 - May 7 1999 (Sattar *et al.*, 2008)	*n* = 4,812 (recruited if had pre-existing vascular disease or raised risk) 70 -82 y	4.0 y (max) [209 without evidence of prevalent vascular disease]	Age, sex, country, & treatment allocation.	<30.0 ≥30.0 [Not reported]	1.00 2.51 (1.89, 3.34)

* Cut points for BMI men, 24.5, 27.3 kg/m ^{2} and women, 23.8, 27.5 kg/m^2

Table S5.5 | Baseline characteristics of the sample including those with missing details

	Age group (years)				
	60 to 64	**65 to 69**	**70 to 74**	**75 to 84**	**≥85**
n	151,736	132,477	115,155	117,003	22,526
Follow up years, mean (SD)	8.4 (3.0)	8.5 (2.9)	8.4 (2.8)	8.1 (2.7)	6.7 (2.1)
Age years, mean (SD)	61.9 (1.5)	66.9 (1.5)	71.8 (1.5)	78.0 (2.7)	87.1 (2.3)
Gender					
Females, n (%)	82,035 (54.1)	70,840 (53.5)	63,539 (55.2)	70,336 (60.1)	15,505 (68.8)
BMI (kg/m^2), mean (SD)	28.2 (5.2)	28.0 (5.0)	27.5 (4.8)	26.5 (4.5)	24.9 (4.2)
BMI (kg/m^2) (%)					
Underweight 14.0 to <18.5	1,017 (0.7)	972 (0.7)	1,252 (1.1)	2,354 (2.0)	1,052 (4.7)
Normal weight 18.5 to <25.0	40,436 (26.7)	36,223 (27.3)	34,215 (29.7)	43,601 (37.3)	11,227 (49.8)
Overweight 25.0 to <30.0	62,780 (41.4)	56,387 (42.6)	49,353 (42.9)	47,885 (40.9)	7,698 (34.2)
Obese-1 30.0 to < 35.0	32,163 (21.2)	27,345 (20.6)	22,126 (19.2)	17,802 (15.2)	2,138 (9.5)
Obese- 2 35.0 to < 40.0	10,705 (7.1)	8,297 (6.3)	6,211 (5.4)	4,269 (3.7)	411 (1.8)
Obese-3 ≥40.0	4,635 (3.1)	3,253 (2.5)	1,998 (1.7)	1,092 (0.9)	

Table S5.5 continued

	60 to 64	65 to 69	70 to 74	75 to 84	≥85
Alcohol Status, n (%)					
Non-drinker	15,746 (10.4)	15,885 (12.0)	15,305 (13.3)	17,906 (15.3)	4,181 (18.6)
Current drinker	90,522 (59.7)	78,654 (59.4)	68,392 (59.4)	68,602 (58.6)	12,814 (56.9)
Ex drinker	2,540 (1.7)	2,584 (2.0)	2,455 (2.1)	2,731 (2.3)	645 (2.9)
Heavy drinker	18,918 (12.5)	14,833 (11.2)	10,941 (9.5)	8,171 (7.0)	1,096 (4.9)
Not recorded	24,010 (15.8)	20,521 (15.5)	18,062 (15.7)	19,593 (16.8)	3,790 (16.8)
Smoking Status, n (%)					
Never	92,957 (61.3)	79,023 (59.7)	67,949 (59.0)	68,131 (58.2)	13,749 (61.0)
Ex-smoker	49,901 (32.9)	46,025 (34.7)	40,671 (35.3)	40,953 (35.0)	7,394 (32.8)
Not recorded	8,878 (5.9)	7,429 (5.6)	6,535 (5.7)	7,919 (6.8)	1,383 (6.1)
Index of multiple deprivation quintiles, n (%)					
1 (least deprived)	40,060 (26.4)	33,952 (25.6)	28,801 (25.0)	27,852 (23.8)	4,959 (22.0)
2	40,703 (26.8)	35,288 (26.6)	30,308 (26.3)	30,072 (25.7)	5,840 (25.9)

Table S5.5 continued

	60 to 64	65 to 69	70 to 74	75 to 84	≥85
IMD quintiles continued 3	31,933 (21.1)	28,005 (21.1)	24,243 (21.1)	24,933 (21.3)	4,851 (21.5)
4	25,168 (16.6)	22,653 (17.1)	20,285 (17.6)	21,690 (18.5)	4,390 (19.5)
5	13,861 (9.1)	12,572 (9.5)	11,506 (10.0)	12,444 (10.6)	2,480 (11.0)
Not recorded	11 (0.0)	7 (0.0)	12 (0.0)	12 (0.0)	6 (0.0)
Diagnosed disease at baseline, n (%)					
Diabetes	14,374 (9.5)	15,157 (11.4)	14,560 (12.6)	12,918 (11.0)	2,349 (10.4)
Coronary Heart Disease	5,650 (3.7)	6,584 (5.0)	7,040 (6.1)	7,421 (6.3)	1,560 (6.9)
Weight stability (4 years prior to BMI record) subgroup, n (%)	68,528 (45.2)	63,179 (47.7)	56,881 (49.4)	53,704 (45.9)	11,408 (50.6)
Weight stable (weight loss or gain of 0 to <5.0 kg) in subgroup	52,908 (77.2)	50,190 (79.4)	46,651 (82.0)	44,399 (82.7)	9,469 (83.0)
Weight loss of ≥5 kg in subgroup	5,800 (8.5)	5,146 (8.1)	4,414 (7.8)	4,749 (8.8)	1,285 (11.3)
Weight gain of ≥5 kg in subgroup	9,820 (14.3)	7,843 (12.4)	5,816 (10.2)	4,556 (8.5)	654 (5.7)

Table S5.6 | Distribution of Outcomes for 'healthier ages' complete cases

Complete cases	Age group (years)				
	60 to 64 [a]	**65 to 69** [a]	**70 to 74** [a]	**75 to 84** [a]	**≥85** [a]
Deaths	7363/124960 (5.9)	11684/109560 (10.7)	17217/95001 (18.1)	34437/94957 (36.3)	10789/18341 (58.8)
Incident CHD	4436/117022 (3.8)	5624/99778 (5.6)	6069/84331 (7.2)	7557/83399 (9.1)	1272/15845 (8.0)
Incident diabetes	5731/106570 (5.4)	5699/90449 (6.3)	4604/76813 (6.0)	3895/79087 (4.9)	456/15660 (2.9)

[a] Cell contents: events/number, (%)

Note: Complete cases were patients without missing values for alcohol status, smoking, or Index of Multiple Deprivation Index. 'Healthier agers' excluded current smokers plus patients with multi-morbidity, heart failure, dementia, or recent cancer at baseline and included follow up from 4 to 14.9 years.

Table S5.7 | Distribution of Outcomes for 'healthier ages' including patients with missing alcohol, smoking, and socioeconomic records

	Age group (years)				
Missing alcohol, smoking or socioeconomic records	**60 to 64** [a]	**65 to 69** [a]	**70 to 74** [a]	**75 to 84** [a]	**≥85** [a]
Deaths	9095/151736 (6.0)	14289/132477 (10.8)	21062/115155 (18.3)	42459/117003 (36.3)	13333/22526 (59.2)
Incident CHD	5272/142331 (3.7)	6682/121151 (5.5)	7236/102815 (7.0)	9101/103328 (8.8)	1518/19570 (7.8)
Incident diabetes	6901/128927 (5.4)	6800/108922 (6.2)	5505/92812 (5.9)	4729/96949 (4.9)	538/19115 (2.8)

[a] Cell contents: events/number, (%)
Note: Complete cases were patients without missing values for alcohol status, smoking, or Index of Multiple Deprivation. 'Healthier agers' subgroup excluded current smokers plus patients with multi-morbidity, heart failure, dementia, or recent cancer at baseline and first 3.9 years of follow-up.

Table S5.8 | Hazard ratios for mortality by BMI category and age-group using BMI high Normal as the reference

	Age group (years)				
BMI categories	**60 to 64** [a]	**65 to 69** [a]	**70 to 74** [a]	**75 to 84** [a]	**≥85** [a]
Underweight	69/767	124/3744	284/958	940/1728	581/791
14.0 to <18.5	2.41 (1.89, 3.08)	2.29 (1.91, 2.75)	2.03 (1.80, 2.30)	1.76 (1.64, 1.89)	1.46 (1.34, 1.60)
Low Normal weight	739/14777	1274/12950	2363/12402	7275/17574	3303/5266
18.5 to <23.0	1.21 (1.09, 1.33)	1.14 (1.06, 1.23)	1.15 (1.09, 1.22)	1.18 (1.14, 1.22)	1.10 (1.04, 1.16)
High Normal weight	878/18654	1632/17144	2732/15681	6457/17666	2281/3847
23.0 to <25.0	1.00	1.00	1.00	1.00	1.00
Low Overweight	1186/22977	1995/20536	3136/18592	6441/18581	1862/3294
25.0 to <27.0	1.05 (0.96, 1.15)	0.97 (0.91, 1.04)	0.95 (0.90, 1.00)	0.96 (0.93, 1.00)	0.91 (0.86, 0.97)
High Overweight	1686/29399	2750/26452	3935/22655	6963/20781	1659/3066
27.0 to <30.0	1.17 (1.08, 1.27)	1.05 (0.98, 1.11)	0.99 (0.94, 1.04)	0.97 (0.94, 1.00)	0.89 (0.83, 0.94)
Obese-1	1714/26177	2602/22475	3351/18118	4842/14379	915/1758
30.0 to < 35.0	1.36 (1.25, 1.48)	1.24 (1.16, 1.32)	1.13 (1.07, 1.18)	1.06 (1.02, 1.10)	0.94 (0.87, 1.01)
Obese-2	2691/8601	844/6685	1035/5031	1176/3379	188/319
35.0 to < 40.0	1.84 (1.67, 2.04)	1.48 (1.36, 1.61)	1.42 (1.32, 1.53)	1.25 (1.18, 1.34)	0.96 (0.83, 1.11)
Obese-3	400/3608	463/2574	381/1564	343/869	
≥40.0	2.73 (2.42, 3.07)	2.32 (2.09, 2.57)	1.92 (1.73, 2.14)	1.71 (1.53, 1.91)	

Healthier agers' subgroup excluded current smokers plus patients with multi-morbidity, heart failure, dementia, or recent cancer at baseline and first 3.9 years of follow-up.

Table S5.9 | Death Rates for 'healthier agers' by BMI category for those aged 65 to 69 years at baseline using the CPRD

BMI Category	0 to 3.9 years [a]	≥4 years [a]
<18.5	11.1	49.5
18.5 to <23.0.	3.8	27.0
23.0 to <25.0	2.9	23.4
25.0 to <27.0	2.6	23.0
27.0 to <30.0	2.6	24.3
30.0 to <35.0	3.0	27.9
35.0 to <40.0	3.6	32.6
≥40.0	4.7	45.2

[a] *Cell contents death %*

Note: 'Healthier agers' were defined as non-smokers, without recent cancer (within the five previous years except non-melanoma skin cancer), dementia, heart failure, or multi-morbidity. Cox proportional hazards models were adjusted for age, gender, alcohol status, smoking status, calendar year, and Index Multiple of Deprivation.

Table S5.9 | Effective age estimates from the reported mortality hazard ratios for 'healthier agers' using BMI high Normal as the reference

	Age group (years)				
BMI categories	**60 to 64** [a]	**65 to 69** [a]	**70 to 74** [a]	**75 to 84** [a]	**≥85** [a]
Underweight 14.0 to <18.5	8.50	7.16	5.82	4.45	3.95
Low Normal weight 18.5 to <23.0	1.82	1.14	1.17	1.27	1.01
High Normal weight 23.0 to <25.0	0.00	0.00	0.00	0.00	0.00
Low Overweight 25.0 to <27.0	0.46	-0.22	-0.44	-0.29	-0.96
High Overweight 27.0 to <30.0	1.51	0.40	-0.09	-0.25	-1.25
Obese-1 30.0 to < 35.0	2.97	1.84	0.97	0.44	-0.67
Obese-2 35.0 to < 40.0	5.91	3.39	2.89	1.78	-0.42
Obese-3 ≥40.0	9.68	7.26	5.36	4.22	

Healthier agers' subgroup excluded current smokers plus patients with multi-morbidity, heart failure, dementia, or recent cancer at baseline and first 3.9 years of follow-up.

Table S5.10 | Competing sub-hazard ratios for incident type 2 diabetes for 'healthier agers' by age-group using BMI high Normal as the reference

	Age group (years)				
BMI categories	**60 to 64** [a]	**65 to 69** [a]	**70 to 74** [a]	**75 to 84** [a]	**≥85** [a]
Underweight	4/740	7/704	13/898	31/1645	14/744
14.0 to <18.5	0.23 (0.08, 0.60)	0.33 (0.15, 0.69)	0.37 (0.21, 0.65)	0.54 (0.37, 0.77)	0.74 (0.42, 1.31)
Low Normal weight	205/14027	260/12001	306/11250	440/15985	102/4764
18.5 to <23.0	0.60 (0.50, 0.70)	0.69 (0.59, 0.80)	0.72 (0.62, 0.83)	0.78 (0.68, 0.88)	0.84 (0.63, 1.11)
High Normal weight	456/17270	506/15401	525/13658	554/15518	85/3358
23.0 to <25.0	1.00	1.00	1.00	1.00	1.00
Low Overweight	736/20597	839/17714	796/15614	764/15584	83/2752
25.0 to <27.0	1.33 (1.18, 1.49)	1.42 (1.27, 1.58)	1.32 (1.19, 1.48)	1.39 (1.25, 1.56)	1.21 (0.89, 1.63)
High Overweight	1422/25031	1552/21660	1236/17989	1013/16774	102/2477
27.0 to <30.0	2.16 (1.95, 2.40)	2.20 (1.99, 2.43)	1.81 (1.64, 2.01)	1.77 (1.59, 1.96)	1.68 (1.25, 2.24)
Obese-1	1854/20534	1718/16938	1206/13163	831/10783	48/1343
30.0 to < 35.0	3.60 (3.24, 3.98)	3.28 (2.97, 3.62)	2.53 (2.29, 2.81)	2.36 (2.12, 2.64)	1.54 (1.08, 2.21)
Obese-2	726/6089	576/4487	411/3325	217/2250	22/222
35.0 to < 40.0	5.22 (4.64, 5.87)	4.48 (3.97, 5.06)	3.73 (3.27, 4.25)	3.05 (2.60, 3.57)	4.23 (2.63, 6.81)
Obese-3	328/2282	241/1544	111/916	45/548	
≥40.0	6.58 (5.69, 7.61)	5.73 (4.90, 6.69)	3.72 (3.02, 4.59)	2.61 (1.93, 3.55)	

Healthier agers' subgroup excluded current smokers plus patients with multi-morbidity, heart failure, dementia, or recent cancer at baseline and first 3.9 years of follow-up. Those with prevalent type 2 diabetes were excluded.

Table S5.12 | Competing sub-hazard ratios for incident coronary heart disease for 'healthier agers' by age-group using BMI high Normal as the reference

	Age group (years)				
BMI categories	**60 to 64** [a]	**65 to 69** [a]	**70 to 74** [a]	**75 to 84** [a]	**≥85** [a]
Underweight	14/745	31/708	50/892	114/1604	35715
14.0 to <18.5	0.68 (0.40, 1.16)	1.03 (0.72, 1.47)	0.88 (0.66, 1.17)	0.81 (0.67, 0.98)	0.63 (0.44, 0.89)
Low Normal weight	341/14255	489/12193	682/11342	1274/15753	362/4645
18.5 to <23.0	0.83 (0.72, 0.95)	0.89 (0.80, 1.00)	0.94 (0.85, 1.04)	0.91 (0.85, 0.98)	1.02 (0.87, 1.19)
High Normal weight	574/17699	771/15822	947/14115	1405/15623	258/3361
23.0 to <25.0	1.00	1.00	1.00	1.00	1.00
Low Overweight	803/21561	1062/18723	1192/16446	1511/16158	233/2775
25.0 to <27.0	1.10 (0.99, 1.22)	1.12 (1.02, 1.23)	1.07 (0.98, 1.16)	1.06 (0.98, 1.14)	1.10 (0.92, 1.31)
High Overweight	1132/27284	1468/23844	1543/19847	1753/18062	248/2608
27.0 to <30.0	1.22 (1.10, 1.35)	1.21 (1.11, 1.33)	1.16 (1.07, 1.26)	1.13 (1.05, 1.21)	1.27 (1.07, 1.52)
Obese-1	1054/24179	1296/20119	1256/15854	1168/12441	111/1463
30.0 to < 35.0	1.32 (1.19, 1.46)	1.34 (1.22, 1.46)	1.24 (1.14, 1.35)	1.15 (1.06, 1.24)	1.07 (0.86, 1.34)
Obese-2	366/7966	377/6051	321/4446	262/2987	25/278
35.0 to < 40.0	1.52 (1.33, 1.73)	1.38 (1.22, 1.57)	1.22 (1.07, 1.38)	1.13 (0.99, 1.29)	1.17 (0.77, 1.77)
Obese-3	152/3333	130/2318	78/1389	70/771	
≥40.0	1.57 (1.31, 1.88)	1.29 (1.07, 1.56)	1.00 (0.80, 1.27)	1.26(0.99, 1.60)	

Healthier agers' subgroup excluded current smokers plus patients with multi-morbidity, heart failure, dementia, or recent cancer at baseline and first 3.9 years of follow-up. Those with prevalent coronary heart disease were excluded.

Table S5.13 | Hazard ratios for mortality by BMI category and age-group using BMI high Normal as the reference with the inclusion of an activity variable

	Age group (years)				
BMI categories	**60 to 64 [a]**	**65 to 69 [a]**	**70 to 74 [a]**	**75 to 84 [a]**	**≥85 [a]**
Underweight	38/410	53/365	124/487	472/882	297/410
14.0 to <18.5	2.72 (1.95, 3.79)	2.15 (1.63, 2.84)	1.77 (1.47, 2.13)	1.89 (1.72, 2.09)	1.63 (1.44, 1.86)
Low Normal weight	383/8286	692/7349	1267/6866	3840/9553	1773/2916
18.5 to <23.0	1.17 (1.02, 1.33)	1.16 (1.05, 1.28)	1.17 (1.09, 1.27)	1.18 (1.13, 1.24)	1.17 (1.08, 1.25)
High Normal weight	483/10639	879/9760	1468/8851	3464/10023	1213/2173
23.0 to <25.0	1.00	1.00	1.00	1.00	1.00
Low Overweight	629/12953	1122/11707	1680/10658	3450/10518	1017/1851
25.0 to <27.0	1.03 (0.92, 1.16)	1.03 (0.94, 1.13)	0.93 (0.87, 1.00)	0.97 (0.93, 1.02)	0.99 (0.91, 1.08)
High Overweight	867/16334	1481/14798	2148/12932	3772/11712	896/1744
27.0 to <30.0	1.13 (1.01, 1.26)	1.09 (1.00, 1.18)	1.00 (0.94, 1.07)	1.00 (0.96, 1.05)	0.90 (0.83, 0.98)
Obese-1	832/14071	1342/12110	1818/9980	2554/8025	475/970
30.0 to < 35.0	1.31 (1.17, 1.46)	1.29 (1.18, 1.40)	1.19 (1.11, 1.28)	1.08 (1.02, 1.14)	1.02 (0.92, 1.13)
Obese-2	325/4523	383/3465	517/2687	600/1834	105/182
35.0 to < 40.0	1.82 (1.58, 2.10)	1.48 (1.31, 1.67)	1.43 (1.29, 1.58)	1.30 (1.19, 1.42)	1.02 (0.83, 1.25)
Obese-3	191/1830	232/1325	194/860	171/479	
≥40.0	2.93 (2.47, 3.47)	2.53 (2.18, 2.93)	2.01 (1.73, 2.34)	1.59 (1.37, 1.86)	

Healthier agers' subgroup excluded current smokers plus patients with multi-morbidity, heart failure, dementia, or recent cancer at baseline and first 3.9 years of follow-up.

Table S5.14 | Hazard ratios for mortality by BMI category and age-group using BMI high Normal as the reference restricted to patients with a 'white' ethnicity record

	Age group (years)				
BMI categories	**60 to 64** [a]	**65 to 69** [a]	**70 to 74** [a]	**75 to 84** [a]	**≥85** [a]
Underweight	60/580	102/581	246/765	821/1498	503/690
14.0 to <18.5	2.50 (1.92, 3.25)	2.30 (1.88, 2.81)	2.12 (1.85, 2.41)	1.78 (1.65, 1.92)	1.49 (1.35, 1.64)
Low Normal weight	637/11207	1096/10353	2064/10297	6326/14988	2758/4483
18.5 to <23.0	1.22 (1.10, 1.36)	1.15 (1.06, 1.25)	1.16 (1.10, 1.23)	1.18 (1.14, 1.22)	1.08 (1.02, 1.15)
High Normal weight	755/14369	1404/13847	2380/13109	5725/15632	1978/3356
23.0 to <25.0	1.00	1.00	1.00	1.00	1.00
Low Overweight	1013/18047	1716/16751	2740/15653	5666/16118	1636/2901
25.0 to <27.0	1.02 (0.92, 1.12)	0.96 (0.90, 1.04)	0.94 (0.89, 1.00)	0.96 (0.93, 1.00)	0.92 (0.86, 0.98)
High Overweight	1442/23302	2418/21767	3480/19267	6150/18133	1450/2718
27.0 to <30.0	1.13 (1.03, 1.23)	1.05 (0.98, 1.12)	0.98 (0.93, 1.03)	0.96 (0.92, 0.99)	0.89 (0.83, 0.95)
Obese-1	1472/20988	2280/18694	2985/15429	4324/12636	798/1531
30.0 to < 35.0	1.30 (1.19, 1.41)	1.21 (1.14, 1.30)	1.13 (1.07, 1.19)	1.05 (1.01, 1.09)	0.96 (0.88, 1.04)
Obese-2	600/7006	723/5588	920/4289	1024/2913	155/275
35.0 to < 40.0	1.76 (1.58, 1.96)	1.40 (1.28, 1.54)	1.42 (1.31, 1.53)	1.22 (1.15, 1.31)	0.91 (0.77, 1.07)
Obese-3	359/3040	418/2200	334/1328	290/754	
≥40.0	2.61 (2.30, 2.96)	2.27 (2.03, 2.54)	1.91 (1.70, 2.14)	1.65 (1.46, 1.86)	

Healthier agers' subgroup excluded current smokers plus patients with multi-morbidity, heart failure, dementia, or recent cancer at baseline and first 3.9 years of follow-up.

Table S5.15 | Hazard ratios for mortality by BMI category and age-group using BMI high Normal as the reference with the exclusion of patients with measured weight loss ≥5kg in the weight stability subgroup

	Age group (years)				
BMI categories	**60 to 64** [a]	**65 to 69** [a]	**70 to 74** [a]	**75 to 84** [a]	**≥85** [a]
Underweight	24/260	39/248	92/337	281/572	185/289
14.0 to <18.5	2.68 (1.77, 4.06)	2.28 (1.65, 3.15)	2.05 (1.65, 2.53)	1.71 (1.51, 1.94)	1.44 (1.23, 1.68)
Low Normal weight	233/5349	432/4908	815/4857	2370/6414	1241/2264
18.5 to <23.0	1.12 (0.94, 1.32)	1.14 (1.01, 1.29)	1.11 (1.01, 1.21)	1.13 (1.07, 1.20)	1.08 (0.99, 1.17)
High Normal weight	313/6962	609/6959	1085/6799	2494/7427	973/1872
23.0 to <25.0	1.00	1.00	1.00	1.00	1.00
Low Overweight	441/9277	836/9063	1345/8804	2705/8570	854/1677
25.0 to <27.0	0.98 (0.84, 1.13)	1.00 (0.90, 1.11)	0.93 (0.86, 1.01)	0.96 (0.91, 1.02)	0.94 (0.86, 1.03)
High Overweight	769/13234	1257/12674	1814/11530	3113/10128	803/1645
27.0 to <30.0	1.19 (1.04, 1.36)	1.08 (0.98, 1.19)	0.97 (0.90, 1.05)	0.99 (0.94, 1.05)	0.92 (0.84, 1.01)
Obese-1	816/13259	1298/11935	1694/10062	2253/7519	465/986
30.0 to < 35.0	1.28 (1.12, 1.46)	1.26 (1.14, 1.39)	1.09 (1.01, 1.18)	1.06 (1.00, 1.12)	1.00 (0.90, 1.12)
Obese-2	361/4905	461/3996	571/3005	611/1947	107/186
35.0 to < 40.0	1.70 (1.46, 1.97)	1.43 (1.27, 1.62)	1.39 (1.26, 1.54)	1.32 (1.21, 1.44)	1.02 (0.83, 1.24)
Obese-3	238/2267	285/1626	227/989	181/515	
≥40.0	2.67 (2.25, 3.16)	2.43 (2.11, 2.80)	2.00 (1.73, 2.31)	1.70 (1.46, 1.98)	

Healthier agers' subgroup excluded current smokers plus patients with multi-morbidity, heart failure, dementia, or recent cancer at baseline and first 3.9 years of follow-up.

Table S5.16 | Hazard ratios for mortality by BMI category and age-group using BMI high Normal as the reference with the exclusion of patients with measured weight loss ≥2.5kg in the weight stability subgroup

	Age group (years)				
BMI categories	**60 to 64** [a]	**65 to 69** [a]	**70 to 74** [a]	**75 to 84** [a]	**≥85** [a]
Underweight	21/202	26/177	67/240	194/415	120/188
14.0 to <18.5	3.05 (1.95, 4.76)	2.11 (1.42, 3.13)	2.16 (1.68, 2.77)	1.63 (1.41, 1.89)	1.39 (1,14, 1.69)
Low Normal weight	184/4444	339/3973	639/3924	1838/5028	945/1720
18.5 to <23.0	1.09 (0.90, 1.32)	1.14 (0.99, 1.31)	1.13 (1.02, 1.25)	1.14 (1.07, 1.22)	1.04 (0.95, 1.15)
High Normal weight	263/5953	498/5829	883/5745	2026/6118	777/1484
23.0 to <25.0	1.00	1.00	1.00	1.00	1.00
Low Overweight	372/8150	697/7844	1128/7549	2314/7362	704/1408
25.0 to <27.0	0.95 (0.81, 1.11)	0.98 (0.87, 1.10)	0.95 (0.87, 1.04)	0.97 (0.92, 1.03)	0.88 (0.80, 0.98)
High Overweight	658/11768	1114/11260	1616/10239	2695/8851	682/1401
27.0 to <30.0	1.14 (0.99, 1.32)	1.11 (1.00, 1.23)	1.01 (0.93, 1.10)	1.01 (0.95, 1.07)	0.90 (0.81, 0.99)
Obese-1	719/11923	1164/10806	1515/9050	2002/6709	397/852
30.0 to < 35.0	1.26 (1.09, 1.45)	1.29 (1.16, 1.43)	1.14 (1.05, 1.24)	1.08 (1.02, 1.15)	0.95 (0.84, 1.07)
Obese-2	323/4473	407/3610	520/2734	535/1750	96/164
35.0 to < 40.0	1.68 (1.42, 1.98)	1.44 (1.26, 1.64)	1.46 (1.31, 1.63)	1.32 (1.20, 1.45)	1.03 (0.83, 1.27)
Obese-3	220/2103	259/1504	207/906	171/475	
≥40.0	2.70 (2.25, 3.24)	2.46 (2.11, 2.86)	2.13 (1.83, 2.48)	1.80 (1.54, 2.11)	

Healthier agers' subgroup excluded current smokers plus patients with multi-morbidity, heart failure, dementia, or recent cancer at baseline and first 3.9 years of follow-up.

Table S5.17 | Hazard ratios for mortality by BMI category and age-group using BMI high Normal as the reference with multiple imputation of missing smoking and alcohol records

	Age group (years)				
BMI categories	**60 to 64** [a]	**65 to 69** [a]	**70 to 74** [a]	**75 to 84** [a]	**≥85** [a]
Underweight	110/1017	183/972	372/1252	1271/2354	753/1049
14.0 to <18.5	3.02 (2.48, 3.67)	2.59 (2.22, 3.01)	2.06 (1.85, 2.30)		1.49 (1.38, 1.62)
Low Normal weight	960/18030	1591/15773	2970/15350	8992/21958	4092/6516
18.5 to <23.0	1.30 (1.19, 1.42)	1.18 (1.11, 1.26)	1.18 (1.12, 1.24)		1.12 (1.06, 1.17)
High Normal weight	1039/22401	1932/20446	3290/18858	7846/21634	2802/4708
23.0 to <25.0	1.00	1.00	1.00		1.00
Low Overweight	1456/27407	2411/24616	3740/22162	7862/22555	2262/4002
25.0 to <27.0	1.09 (1.00, 1.18)	0.98 (0.93, 1.04)	0.94 (0.90, 0.98)		0.92 (0.87, 0.98)
High Overweight	2033/35370	3323/31770	4768/27187	8523/25328	2035/3696
27.0 to <30.0	1.17 (1.08, 1.26)	1.05 (0.99, 1.11)	0.99 (0.95, 1.04)		0.91 (0.86, 0.97)
Obese-1	2114/32161	3199/27343	4120/22126	6044/17801	1135/2138
30.0 to < 35.0	1.36 (1.27, 1.47)	1.24 (1.17, 1.31)	1.12 (1.07, 1.17)		0.96 (0.90, 1.03)
Obese-2	853/10704	1071/8297	1301/6210	1483/4269	248/411
35.0 to < 40.0	1.82 (1.66, 1.99)	1.49 (1.39, 1.61)	1.41 (1.32, 1.50)		1.00 (0.87, 1.13)
Obese-3	527/4635	576/3253	497/1998	428/1092	
≥40.0	2.79 (2.51, 3.11)	2/27 (2.07, 2.50)	1.92 (1.75, 2.11)		

Healthier agers' subgroup excluded current smokers plus patients with multi-morbidity, heart failure, dementia, or recent cancer at baseline and first 3.9 years of follow-up.

Chapter 6 The association between BMI and incident dementia

Table of Contents

List of Tables for Chapter 6

List of Figures for Chapter 6

6.1. Summary

Background: The risk for dementia for those within the body mass index (BMI) defined Obese range (BMI ≥30.0 kg/m^2) in later life is unclear, with reduced, non-significant, and increased risks reported relative to those within the BMI Normal range (BMI 18.5-24.9 kg/m^2). Weight loss has been reported to precede the clinical diagnosis of dementia within the previous decade. Dementia risks may be distorted due to the chosen BMI referent group and the years of follow-up excluded to minimise reverse causality.

Objective: To estimate pre-diagnosis weight loss in those diagnosed with dementia. Secondly to estimate the associations between BMI and dementia for the short (0 to <10 years) and long (10 to <14.9years) term.

Design: This analysis included 257,523 'healthier agers' (from 1st January 2000) aged 65 to 74 years using primary care, hospital and death certificate electronic health records from the Clinical Practice Research Datalink (CPRD). 'Healthier agers' are defined as non-smokers without dementia or additional conditions associated with weight loss. Competing risks models were used with adjustment for age, gender, alcohol use, smoking history, calendar year and socioeconomic status.

Results: During a maximum follow-up period of 14.9 years there were 9,774 incident cases of dementia and 29,466 deaths. Weight loss of ≥2.5 kg was documented in 54% of those with repeat measures, and with a dementia diagnosis. In the short-term (0 to <10 years), there were reduced risks for incident dementia for those within the BMI Overweight (sub Hazard Ratio [SHR] 0.80 95% Confidence Interval [CI] 0.75, 0.85) and BMI Obese range (SHR 0.69 CI 0.65, 0.74) relative to those within the BMI 22.5 to <25.0 kg/m^2 range. However, there was a reversal of the risks in the long term (10 to 14.9 years) with an increased risk for those for the BMI Obese range (SHR 1.17 CI 1.03, 1.32), and the risks for those within the BMI Overweight range were not significantly different.

Conclusions: This analysis showed that the risks for incident dementia for those within the BMI Obese range relative to those within the BMI 22.5 to <25.0 kg/m^2 range were markedly altered after excluding incident dementia and deaths occurring within the first decade. Persons with obesity are at increased dementia risk in the longer term. Paradoxical risks (i.e. reduced risks) for dementia for those within the BMI Obese range in later life could reflect weight loss in the decade before diagnosis.

6.2. Introduction

Dementia is a key public health issue. Globally, the prevalence of dementia was estimated to be 46.8 million in 2015, and is anticipated to reach 131.5 million by 2050 due in part to the increasing proportion of older adults and improved recognition of the syndrome (Prince, 2015). In England, in 2015 Alzheimer's disease was ranked the seventh leading cause of disability adjusted life years, with this ranking increasing with advancing age (Kassebaum *et al.*, 2016). Dementia has a significant impact on the individual's independence and quality of life, and is becoming an increasing financial burden for health and social care providers (World Health Organization, 2012, 2015; Prince, 2015). The role of modifiable risk factors is of great interest as there is currently no cure for dementia.

A reversal of the risks for incident dementia for those within the BMI Obese range relative to those within the BMI Normal range has been reported, with increased risks for dementia in midlife (Kivipelto *et al.*, 2005; Whitmer *et al.*, 2005) and reduced risks for dementia in later life. Pedditzi *et al.*, (2016) reported an increased risk for dementia of 41% (CI 1.20, 1.66) for those within the BMI Obese range relative to those within the BMI Normal range from analyses which included adults aged <65 years from their meta-analysis. In contrast, analyses with a mean participant age of ≥65 years showed a reduced risk for dementia of 17% (CI 0.74, 0.94) for those within the BMI Obese range relative to those within the BMI Normal range. The risk for incident dementia was not significantly different for those within the BMI Overweight range (RR 0.88 CI 0.78, 1.02). Overall there have been a limited number of studies, with four reporting estimates for the BMI Obese range and five for the BMI Overweight range, for incident dementia in later life (Pedditizi, Peters and Beckett, 2016; Pedditzi, Peters and Beckett, 2016).

The proposed explanations for the reversal of BMI risks with dementia show similarities to those suggested for the reversal of BMI risks with mortality in later life. These include selective survival, the use of BMI as a surrogate for adiposity in older persons, attenuation of health risks with advancing age, and reverse causation (Luchsinger *et al.*, 2007; Atti *et al.*, 2008; Fitzpatrick *et al.*, 2009; Tolppanen *et al.*, 2014). Weight loss has been reported to precede the clinical

diagnosis of dementia within the previous decade (Knopman *et al.*, 2007). It follows that the conventional BMI Normal range may contain persons whose BMI has been reduced due to preclinical stages of dementia and thus risk estimates for higher BMI categories may be distorted. In **Chapter 5,** I presented an analysis which estimated the association between continuous BMI and mortality risk in later life. Persons within the BMI 18.5-22.9 kg/m^2 range had increased mortality risks compared to those within the BMI range 23.0-26.9 kg/m^2. Thereby using the conventional BMI Normal range may have distorted the mortality risk estimates for those with higher BMI values.

In the supplementary material tables S1.2 and S1.3 I summarised the association between BMI and incident dementia/associated dementia subtypes for adults aged ≥65 years showing that the findings were equivocal. Discrepancies may be due to the age structure of the analyses, sample sizes, and length of the follow-up (Fitzpatrick *et al.*, 2009; Gustafson *et al.*, 2009). There was a lack of studies reporting estimates for BMI groups and incident dementia in later life, especially for the BMI Overweight and Obese ranges. Many of the studies pooled broad age ranges which may have diluted the dementia risk estimates. A limited number of studies used a competing risk approach to assess the relationship between BMI and incident dementia, which may have led to an underestimation of the reported risks (**Chapter 2**).

One study reported estimates for BMI and incident dementia using different time frames i.e. estimating the risk for dementia after excluding differing years of follow-up. Atti *et al*., (2008) reported that the risk of incident dementia was not substantially different following the exclusion of the first six years relative to the whole nine-year period for adults aged ≥75 years from the Kungsholem Project. However, this analysis was not able to separate those within the BMI Overweight or Obese ranges due to the limited sample size (Atti *et al.*, 2008).

Many of the studies reported within supplementary material Table S1.2 had a baseline period within the 1990s. This necessitates assessing the association between recent measures of BMI and dementia due to improved diagnosis, the prevalence of persons classified as BMI Overweight or Obese, and the proportion of older adults. Here I aimed to estimate pre-diagnosis weight loss in those

diagnosed with dementia. Secondly, I aimed to estimate the associations between BMI and incident dementia for 'healthier agers' aged 65 to 74 years using competing risks models, to estimate short-term (0 to <10 years from baseline BMI measure), and longer-term (10 to <14.9 years). The age range 65 to 74 years was chosen to ensure that this would be late onset dementia and with enough incident cases of dementia. Additionally, there have been no studies which have focused specifically on this age range; using a broader age range may dilute risk estimates due to the combining of the youngest old and oldest old.

6.3. Methods

6.3.1. Study Population

In this chapter I use a similar methodology to **Chapter 4** and **Chapter 5,** using de-identified electronic health records from the CPRD. This includes patients with GP records linked to Hospital Episode Statistics data for admissions (linkage available for England only) and the government's Office for National Statistics (ONS) death certificate data. As emphasised in **Chapters 2** and **4**, registration with GPs is nearly complete in the UK and CPRD diagnostic and outcome coding has generally high validity (Herrett *et al.*, 2010).

6.3.2. 'Healthier agers'

The 'healthier agers' were defined as non-smokers without dementia plus conditions associated with weight loss. The conditions excluded were cancer (excluding non-melanoma skin cancer) within the previous five years, heart failure, and a measure of multi-morbidity. These conditions had been empirically identified as being associated with weight loss which was presented in **Chapter 4**. All patients with BMI records since the 1st January 2000 and registered with a CPRD practice at the time of measurement were included with extreme values of BMI excluded (<14.0 and > 56.5 kg/m^2).

6.3.3. Exposure

The earliest age at which a BMI was recorded was calculated within the age group 65 to 74 years. The first BMI record was included as the study 'index' BMI

for analysis. BMI (kg/m^2) was categorised following the Global BMI Mortality Collaboration groupings (Di Angelantonio, *et al*., 2016) as BMI <18.5, 18.5 to <20.0, 20.0 to <22.5, 25.0 to <30.0, and ≥30.0 kg/m^2.

6.3.4. Lifestyle and socioeconomic variables

Models were adjusted for age, gender, alcohol use, smoking history (never or former), calendar year and socioeconomic status. These variables have been previously defined in **Chapters 2** and **4** and are in line with model adjustments from previous analyses (supplementary material tables S1.2 and S1.3).

6.3.5. Outcomes

Outcomes included incident dementia (from GP records or Hospital Episode Statistics) and mortality (from Office for National Statistics death certificate data) up to the 17th November 2014.

6.3.6. Statistical analysis

Competing risks models (accounting for mortality) were used to estimate the associations between the redefined BMI groups and incident dementia. Multivariate models were adjusted for age, gender, alcohol use, smoking history, calendar year, and socioeconomic status. In a sensitivity analysis participants previously diagnosed with angina, myocardial infarction, or type 2 diabetes were excluded. Analyses were carried out using Stata statistical software (version 13.1) and R statistical software (version 3.1.2.)

6.4. Results

6.4.1. Baseline characteristics

The characteristics of the 257,523 'healthier agers' aged 65 to 74 years at baseline with complete records for smoking history, alcohol status, and socioeconomic status are presented in **Table 6.1**. The mean BMI was 27.7 kg/m^2 (SD 4.9 kg/m^2), and 53.4% of the sample were female.

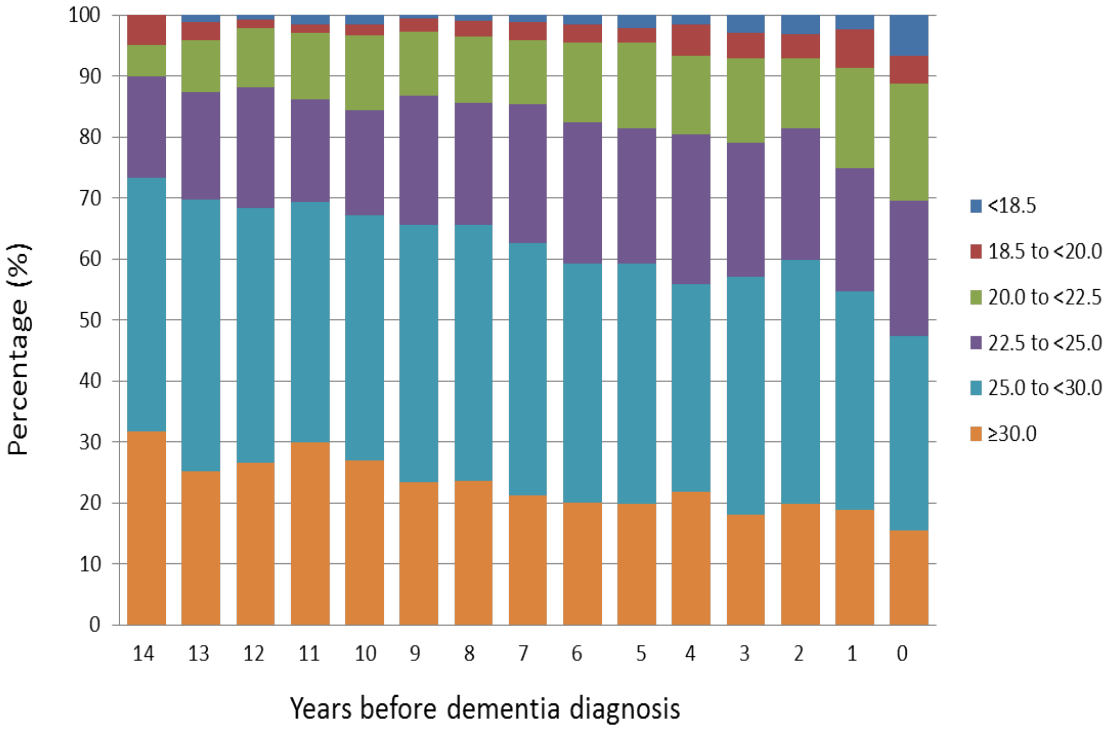
Figure 6.1 shows the BMI proportions for all those diagnosed with dementia (*n* = 9,774) by the number of years to incident disease. This showed lower obesity prevalence in those diagnosed sooner after baseline with 15.5% of those diagnosed with dementia in the first year of follow-up being BMI Obese, compared to 23.4% for those diagnosed in the 9th year of follow-up. Underweight (BMI <18.5 kg/m^2) and leaner BMI Normal weights (18.5 to <20.0 kg/m^2) showed converse changes. Subject weight change was then analysed in those who were diagnosed with dementia by subtracting the median recorded weight in the three years immediately before dementia diagnosis from the median weight eight to ten years before diagnosis. Records allowed weight change calculations for 4,760 (48.7%) with dementia, and of these 67.7% lost weight, with 54.0% loosing ≥2.5kg during the decade before diagnosis.

Table 6.1 | Characteristics of the 'healthier agers' aged 65 to 74 years at baseline from the CPRD

n	**257,523**
Follow-up years, mean (SD)	6.2 (4.1)
Age years, mean (SD)	68.3 (2.9)
Gender	
Females, *n* (%)	137,583 (53.4)
BMI (kg/m^2), mean (SD)	27.7 (4.9)
BMI (kg/m^2), n (%)	
BMI <18.5	2,367 (0.9)
BMI 18.5 to <20.0	4.553 (1.8)
BMI 20.0 to <22.5	22,225 (8.6)
BMI 22.5 to <25.0	48,577 (18.9)
BMI 25.0 to <30.0	109,195 (42.4)
BMI ≥30.0	70,606 (27.4)
Alcohol Status, n (%)	
Non-drinker	38,696 (15.0)
Current drinker	179,839 (69.8)
Ex drinker	34,264 (13.3)
Heavy drinker	4,724 (1.8)
Smoking Status, n (%)	
Never	161,063 (62.5)
Ex-smoker	96,460 (37.5)
Index of multiple deprivation quintiles (1 least deprived; 5th most deprived), n (%)	
1	66,513 (25.8)
2	68,028 (26.4)
3	54,263 (21.1)
4	44,326 (17.2)
5	24,393 (9.5)

Note: 'Healthier agers' were non-smokers without recent cancer (within the previous five years except non-melanoma skin cancer), dementia, heart failure, or multi-morbidity.

Figure 6.1 | Proportion of study sample with incident dementia by BMI categories



Note: 'Healthier agers' were non-smokers without recent cancer (within the previous five years except non-melanoma skin cancer), dementia, heart failure, or multi-morbidity.

6.4.2. BMI categorical associations with dementia

There were 9,774 incident cases of dementia and 29,466 deaths during a maximum follow-up period of 14.9 years. The BMI range 22.5 to <25.0 kg/m^2 was used as the referent group. Estimates for dementia were derived for the short (0 to <10 years from baseline measure) and long (10 to <14.9 years) term.

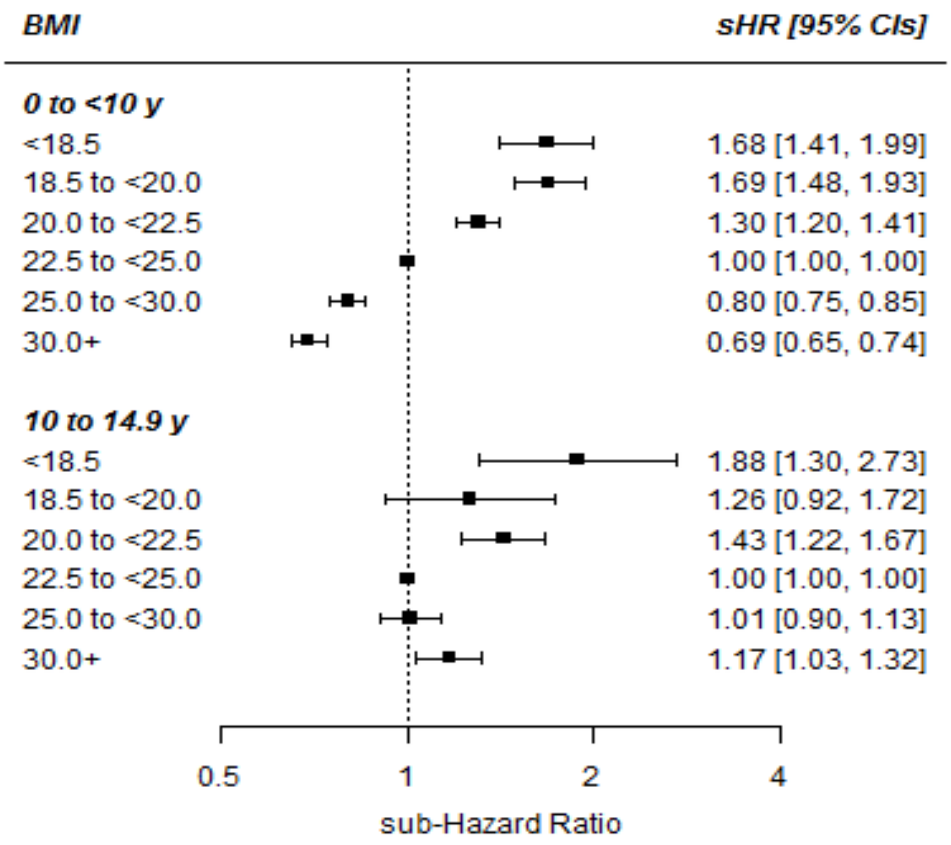
From analysis baseline to <10 years of follow-up (**Figure 6.2),** there was a reduced risk for incident dementia for those within the BMI Obese range (SHR 0.69 95% CI 0.65, 0.74) and BMI Overweight range (SHR 0.80 CI 0.75, 0.85) relative to those within the BMI 22.5 to <25.0 kg/m^2 range. However, for the longer-term follow-ups (between 10 and 14.9 years from baseline), there was an increased risk of incident dementia for the BMI Obese range (SHR, 1.17; 95% CI, 1.03, 1.32). The dementia risk for BMI Overweight range was not significantly

different to that of the referent range. In models pooling shorter and longer follow-ups (supplementary material table S6.1), the shorter term protective associations predominated, although with smaller overall sub-Hazard Ratios than for the 0 to <10 year period only. Low BMIs were consistently associated with increased risks of dementia in both the short and long-term.

Sensitivity analysis

In a sensitivity analysis (supplementary material table S6.2), patients with a previous diagnosis of angina, myocardial infarction, or type 2 diabetes were excluded. This reduced the sample size to 49,341 and attenuated the 10 to 14.9 year results only slightly for the BMI Obese range (SHR, 1.16; 95% CI, 1.01,1.33).

Figure 6.2 | sub-Hazard ratios for incident dementia by BMI groups for the short (0 to <10 years) and long (≥10 to 14.9 years) term using competing risks models for 'healthier agers' aged 65 to 74 years (*n* = 257,523) from the CPRD



Note: 'Healthier agers' were non-smokers without recent cancer (within the previous five years except non-melanoma skin cancer), dementia, heart failure, or multi-morbidity.

6.5. Discussion

In this chapter I aimed to estimate pre-diagnosis weight loss in those diagnosed with dementia and secondly to estimate the associations between BMI and dementia for the short (0 to <10 years) and long (10 to <14.9 years) term. Previous work has indicated that weight loss occurs up to ten years before the clinical diagnosis for dementia. I, therefore, hypothesised that excluding this follow-up period would markedly alter the risk for incident dementia. I showed that there was substantial weight loss during the 10 years before dementia diagnosis. There appeared to be a reduced risk for incident dementia for those within the BMI Obese range and BMI Overweight range from 0 to 14.9 years. However, when outcomes from 10 to 14.9 years after baseline were tested, the risk estimate reversed with those within the BMI Obese range having an increased risk for dementia. The risks for those within the BMI Overweight range were not significantly different to those of the referent range. Previous analyses have shown that there is an increased risk for incident dementia for the BMI Obese range in younger and middle aged cohorts; dementia risks for older adults, however, have not been clear. The ability to evaluate the risks for incident dementia for the BMI groups using the short (0 to <10 years) and long term (10 to 14.9 years) is a unique feature of the analysis I have presented in this chapter. Overall, these results contest the notion that persons within the BMI Obese range have a reduced risk of dementia in the longer term. Reports of reduced risks for dementia for those within the BMI Obese range in later life may be due to the long preclinical phase of dementia, during which time weight loss is common.

6.5.1. Comparison to the literature

The reduced dementia risks for those within the BMI Obese range for the whole follow-up period are partly in line with the previous analysis by Fitzpatrick *et al*., (2009). Reduced risks (HR 0.63 CI 0.44, 0.91) for incident dementia were reported for those within the BMI Obese range relative to those within the BMI range 20.0-24.9 kg/m^2 for adults aged 65 to 97 years (n = 2,798) using the Cardiovascular Health Study with a mean follow-up period of 5.4 years (Fitzpatrick *et al.*, 2009). However, the results presented in this chapter for the whole follow-up period contrast with several previous analyses. Hayden *et al*., (2006) documented increased risks for incident dementia for those within the BMI

Obese range (HR 1.76 CI 1.03, 2.88) relative to those outside of the BMI Obese range for adults aged ≥65 years using The Cache County Study of Memory Health and Aging with a five year follow-up period (Hayden *et al.*, 2006). Conversely, Power *et al.*, (2011) found that the risk for dementia was not significantly different for those within the BMI Obese range relative to those within the BMI range <25.0 kg/m^2 for males aged 65 to 84 years from the Health In Men Study with a 13.4 year follow-up period (Power *et al.*, 2011). Similarly, Tolppanen *et al.*, (2014) reported that the risk for dementia was not significantly different for those within the BMI Obese range relative to those within the BMI range <25.0 kg/m^2 for adults aged 65 to 79 years from the Cardiovascular risk, factors, Aging and Dementia study with a maximum of 10 years of follow-up (Tolppanen *et al.*, 2014). It is, however, difficult to compare the results presented in this chapter to prior analyses due to the different age compositions of the samples, model adjustments, statistical models, different BMI referent groups, and the length of follow-up.

The dementia risk estimates derived for the short and long term cannot be compared directly to previous analyses due to a lack of published literature which has reported risk estimates for the age range presented in this chapter. However, Atti *et al.*, (2008) used a slightly older cohort (aged ≥75 years) with the BMI Overweight and BMI Obese ranges combined. For the whole follow-up period (0 to 9 years) those within the BMI Overweight/Obese range had a reduced risk for dementia (HR 0.75 CI 0.59, 0.96) relative to those within the BMI range 20.0-24.9 kg/m^2. After excluding the first six years the dementia risks were not significantly different (HR 0.66 CI 0.40, 1.07), although with wide confidence intervals due to the limited sample size (Atti *et al.*, 2008).

6.5.2. Strengths and limitations

My analysis has added to the limited body of literature that has assessed the impact of obesity on dementia risk estimates for the short and long term using a competing risk approach. Using the BMI range 22.5 to <25.0 as the referent group highlighted the increased risks for dementia for those within the lower end of the BMI Normal range (BMI 18.5 to <22.5 kg/m^2). The conventional BMI Normal range is, therefore, biased with the inclusion of persons within the lower end of

this range. The heightened risk for dementia for those within the conventional BMI Normal range may have led to distortion of dementia risk estimates for higher BMI values for previous analyses. The sample size is much greater than those previously analysed (supplementary material table S1.2).

There are several limitations to my analysis. As noted previously (**Chapters 4** and **5**) the patients analysed in this chapter were predominately British 'white' ethnicity and, therefore, the findings may not be generally applicable to other ethnic groups. These results, like **Chapter 5**, are derived from a group of 'healthier agers'. This group of patients would be the main target for obesity prevention (**Chapter 3**). Risks were estimated for total dementia and, therefore, risks for the different subtypes (Alzheimer's and Vascular Dementia) may differ to those presented in this chapter for total dementia. I was unable to adjust for other risk factors such as head injuries, hearing loss and there was no data available on dietary patterns, early life factors, education or genetics (Kalaria *et al.*, 2008; Flicker, 2010; Lin *et al.*, 2011; Reitz and Mayeux, 2014).

6.6. Conclusions

This analysis showed that the risks for incident dementia for those within the BMI Obese range relative to those within the BMI 22.5 to <25.0 kg/m^2 range were markedly altered after excluding incident dementia and deaths occurring within the first decade. For non-smoking 'healthier agers' aged 65 to 74 yeas obesity is associated with an increased incidence of dementia in the longer-term. Paradoxical risks for dementia for those within the BMI Obese range in later life could be due to the long preclinical phase of dementia.

Supplementary material for Chapter 6

List of Tables for supplementary material for Chapter 6

Table S6.1 | sub-Hazard Ratios for incident dementia for 0 to 14.9 years for 'healthier ages' aged 65 to 74 years at baseline from the Clinical Research Practice Datalink

BMI category	**Sub-Hazard Ratio (95% Confidence Interval)**
BMI <18.5	1.63 (1.40, 1.91)
BMI 18.5 to <20.0	1.58 (1.40, 1.79)
BMI 20.0 to <22.5	1.31 (1.22, 1.41)
BMI 22.5 to <25.0	1.00
BMI 25.0 to <30.0	0.84 (0.80, 0.89)
BMI ≥ 30.0	0.78 (0.73, 0.83)

Note: 'Healthier agers' were non-smokers without recent cancer (within the previous five years except non-melanoma skin cancer), dementia, heart failure, or multi-morbidity.

Table S6.2 | sub-Hazard Ratios for incident dementia for 10 to 14.9 years for 'healthier ages' aged 65 to 74 years at baseline from the Clinical Research Practice Datalink with further exclusion of those with a diagnosis of type 2 diabetes, angina, or myocardial infarction

BMI category	**Sub-Hazard Ratio (95% Confidence Interval)**
BMI <18.5	2.10 (1.45, 3.05)
BMI 18.5 to <20.0	1.27 (0.91, 1.78)
BMI 20.0 to <22.5	1.46 (1.23, 1.73)
BMI 22.5 to <25.0	1.00
BMI 25.0 to <30.0	1.00 (0.88 ,1.13)
BMI ≥ 30.0	1.16 (1.01, 1.33)

Note: 'Healthier agers' were non-smokers without recent cancer (within the previous five years except non-melanoma skin cancer), dementia, heart failure, or multi-morbidity.

Chapter 7 – Comparison of established measures of body fat distribution, components of body composition to BMI for mortality prediction for 'healthier agers' within the seventh decade of life using the UK Biobank

Table of Contents

List of Tables for Chapter 7

List of Figures for Chapter 7

7.1. Summary

Background: Inclusion of smokers and persons with conditions associated with weight loss partly explain the reduced mortality risks reported for the body mass index (BMI) defined Obese range in later life relative to those within the BMI Normal range. BMI, however, does not measure the increase in fat mass or redistribution of fat with ageing; this may additionally contribute to the obesity paradox. Measures of body fat distribution and body composition have been proposed as alternative measures of adiposity although the ability of these measures to predict mortality in later life is uncertain.

Objectives: To assess BMI associations with mortality using the World Health Organization classification. Secondly, to compare established measures of body fat distribution and body composition to BMI for mortality prediction for 'healthier agers' within the seventh decade of life and to describe the concordance between categories of BMI and these different measures.

Design: This analysis included 136,933 'healthier agers' aged 60 to 69 years enrolled in the UK Biobank (baseline 2006-2010). 'Healthier agers' were non-smokers without conditions associated with weight loss (cancer, dementia or heart failure) or reported weight loss and who survived the first two years of follow-up. BMI, body fat distribution (waist circumference [WC], waist-to-hip ratio [WHR] and waist-to-height ratio [WHtR]), and body composition measures (body fat percentage [BF%], fat mass index [FMI], fat free mass index [FFMI] and skeletal mass index [SMI]) were derived from baseline measures. Population and sex-specific tertiles were derived for each measure and Cox proportional hazard models were used to estimate the mortality risks. Adjustments were made for age, sex, alcohol intake, smoking history and education. The Akaike information criterion (AIC) was used to assess the best model fit for mortality.

Results: A total of 3,180 participants died during the follow-up period (≤8.3 years of follow-up). There were increased risks for mortality for the Obese classes relative to those within the conventional BMI Normal range (Obese-1 range, Hazard Ratio 1.24 [HR] 95% Confidence Interval [CI] 1.14, 1.47). The risks for mortality were not significantly different for those within the BMI Overweight range

relative to those within the BMI Normal range. The mortality model fit was substantially improved (lowest AIC values) compared to the BMI model when tertiles of the WC, WHR and WHtR were used. There were increased mortality risks for those within the higher tertiles of WC (HR 1.40 CI 1.28, 1.52), WHR (HR 1.43 CI 1.31, 1.56) and WHtR (HR 1.37 CI 1.25, 1.49) relative to those within the lowest tertile of each measure. The model fit for models containing body fat percentage or FMI were comparable to the BMI model. Models containing FFMI and SMI did not show any improvement on mortality prediction compared to BMI, achieving the highest AIC values. The concordance between tertiles of BMI and tertiles of FMI was high. The lowest concordance was found between tertiles of BMI and WHR tertiles.

Conclusions: Measures of fat distribution (WC, WHR, or WHtR) for 'healthier agers' within the seventh decade of life improved mortality prediction compared to models containing BMI. Persons with higher adiposity (measured overall or centrally) are at a substantially increased risk for mortality. The lowest concordance was found between BMI tertiles and WHR tertiles.

7.2. Introduction

Many clinical practice guidelines endorse BMI to classify persons as overweight or obese (Jensen *et al.*, 2013; NICE Guidelines, 2014). It is well established that younger and middle aged adults with a high BMI are at an increased risk for premature mortality compared to those within the BMI Normal range (Calle *et al.*, 1999; Adams *et al.*, 2006; Whitlock *et al.*, 2009). However, mortality risks for the obese range has been shown to attenuate with advancing age (Calle *et al.*, 1999; Stevens *et al.*, 1999) and reduced risks have even been reported (Al Snih *et al.*, 2007). Inclusion of smokers and those with weight loss associated disease partly explains these findings as shown in **Chapters 3, 4** and **5**. BMI is unable to distinguish between fat and fat free mass and does not measure body fat distribution. As highlighted in **Chapter 1**, changes in body composition occur across the life cycle and the use of BMI for prediction of health outcomes in later life has, therefore, been questioned. Fat mass tends to accumulate and is redistributed centrally with advancing age (Zamboni *et al.*, 2005; Miller and Wolfe, 2008).

Body fat distribution measures (abdominal adiposity) including waist circumference (WC), waist-to-hip ratio (WHR), and waist-to-height ratio (WHtR) have been proposed as alternative measures for assessing health outcomes in later life. Mortality risks associated with each body fat distribution measure have been equivocal. Increased mortality risks during a median follow-up period of eight years have been documented for females aged 60 to 79 years from the British Women's Heart and Health Study for each standard deviation increment in WC, WHR, and WHtR (Taylor *et al.*, 2010). Conversely, no significant mortality associations were reported for WC, WHR, and WHtR from a 22 year follow-up period for adults aged ≥65 years enrolled in the Rotterdam Study (Dhana *et al.*, 2016). Similarly, no significant associations between WC or WHR categories and mortality have been reported for males aged ≥65 years from the Health Professional Follow up Study or for males aged 60 to 79 years from the British Regional Heart Study (Baik *et al.*, 2000; Wannamethee *et al.*, 2007). In contrast, higher levels of WC and WHR were shown to be associated with a reduced mortality risk relative to those within the lowest quintiles for males aged 65 to 102 years enrolled in NHANES III over a 12 year follow-up period. There was a

reduced mortality risk for females within the highest WC quintile relative to those within the lowest quintile. No significant associations were reported for WHR and overall there were no significant trends for WC or WHR for the females (Reis *et al.*, 2009).

Likewise, body composition measures including body fat percentage (BF%), fat mass (FM), fat free mass (FFM), and skeletal mass (SM) have been considered to identify those at higher risk for adverse health outcomes. Mortality associations were U shaped for women aged ≥67 years enrolled in the Study of Osteoporotic Fractures during an eight year follow-up period for lean mass (LM), FM, and BF%. The lowest mortality risk was for those within the third quintile of each measure. Body composition measures (FM, LM, BF%) were not considered superior to the anthropometric measures (BMI or WC) (Dolan *et al.*, 2007). Reduced mortality risks for women aged 60 to 69 years enrolled in the Women's Health Initiative during 13.6 years of follow-up for those within the third and fourth quintile of BF% and the third quintile of lean BF% have also been documented (Bea *et al.*, 2015). In contrast, no associations were reported between tertile measures of BF% or LM with mortality for adults aged ≥60 years (excluding current smokers and those with heart failure, cancer, kidney disease, or respiratory disease) enrolled in NHANES III; the tertiles used in this analysis were not sex specific (Batsis, Singh and Lopez-Jimenez, 2014).

Mortality risks associated with measures of body fat distribution are unclear. There is a paucity of studies which have provided mortality estimates for measures of body composition, with some researchers suggesting that these may not be superior to BMI. Additionally, there has been a limited number of studies which have reported on mortality risks for body fat distribution measures and body composition measures concurrently. The UK Biobank is one of the largest studies to date with bio-impedance measures and abdominal adiposity measures. This dataset offers a unique opportunity to compare established measures of body fat distribution and body composition with mortality for 'healthier agers' within the seventh decade of life. 'Healthier agers' are defined as non-smokers without diseases associated with weight loss (cancer, dementia or heart failure) or reported weight loss and survived the first two years.

7.3. Methods

7.3.1. Participants

A more detailed description of the UK Biobank was presented in **Chapter 2**. Over 500,000 volunteers across England, Wales, and Scotland were enrolled within the UK Biobank between 2006-2010, with most participants aged 40 to 69 years. The overall response rate for the UK Biobank was 5.5% (Allen *et al.*, 2012). Participants aged 60 to 69 years were included in this analysis. This age group was chosen because paradoxical reports for the associations between BMI and mortality have predominately been reported for this age range and older age groups. Although a small number of participants were aged >69 years, these participants were excluded as the UK Biobank set out initially to recruit adults aged 40 to 69 years (UK Biobank, 2007).

Participants were excluded who: (a) were missing BMI records (*n* = 1,299), (b) had a BMI in the underweight range (<18.5 kg/m^2) due to the substantial increased mortality risk relative to the BMI Normal category (HR 2.74 CI 2.22, 3.39 using complete cases *n* = 208,307 adjusted for age, sex, smoking, alcohol intake, and education), (c) were missing waist circumference (*n* =44), hip circumference (*n* = 19), whole body fat mass (n = 3,868), whole body fat free mass (*n* = 4), and impedance of whole body (*n* = 16), (d) were missing responses to smoking status, alcohol intake or educational attainment (*n* = 5,335), (e) were current smokers and/or with a previous diagnosis of cancer, dementia, or heart failure (*n* = 40,679) due to these conditions being associated with weight loss (see **Chapter 4**) and altered body fat distribution; these diagnoses were derived from cancer registries, hospital admissions and responses to the questionnaires at baseline from the participants, (f) were known to have died but missing a death date (*n* =1), (g) died within the first two years of follow up (*n* = 727) to minimize the effects of reverse causation whereby underlying diseases are associated with a lower BMI and increased risk of death and (h) reported at baseline that they had lost weight compared to the previous year or didn't know or preferred not to answer *(n* = 25,252); weight loss has been reported to be associated with increased mortality risks and the degree of weight change or the intentionality of the weight change were not asked at baseline. The resulting group was termed 'healthier agers' (*n* =136,933).

7.3.2. Exposures

During the baseline visit, height, weight, hip circumference and waist circumference measures were obtained using the widest part of the hip and the natural indent of the waist (UK Biobank, 2014). Body mass index (BMI), waist-to-hip ratio (WHR), and waist-to-height ratio (WHtR) were derived from the baseline measures. Body fat percentage, whole body fat mass, whole body fat free mass, and impedance of the whole body were recorded using Tanita BC418MA body composition analyses at baseline (see **Chapter 2**). Fat mass index (FMI) was derived from the whole-body fat mass/ height^2 and the fat free mass index (FFMI) was derived from the whole body fat free mass / height^2. Skeletal mass was derived using the following equation published by Janssen *et al.,* (2000):

> Skeletal mass (kg) = [(Ht^2/*R* x 0.401) + (gender x 3.825) + (age x -0.071)] + 5.102 (Janssen *et al.*, 2000)

Skeletal mass index (SMI) was then derived from the skeletal mass/ height^2. BMI was categorised by the conventional WHO thresholds. Population and sex-specific tertiles were then derived for all exposures.

7.3.3. Lifestyle and education variables

Participants reported their alcohol intake frequency at their baseline visit with the following possible responses: never, one to three times per month, one to two times per week, three to four times per week, and daily/almost daily. Participants were categorised as never or former smokers. Highest educational attainment was defined as: none, CSEs (Certificate of Secondary Education), GCSE's/O-levels (General Certificate of Secondary Education/Ordinary Level taken at age 15 to 16 years), A-levels/NVQ/HND/HNC (Advance level/ National Vocational Qualification/Higher National Diploma/Higher National Certificate, further education after age 16), professional qualification, and college or university degree. Participants were categorised according to their level of physical activity as low, moderate or vigorous. This was derived from participant responses to frequency and duration of walking, moderate activity, and vigorous activity using the validated International Physical Activity Questionnaire. Total metabolic

equivalent (MET) minutes of exercise per week were then derived (Craig *et al.*, 2003).

7.3.4. Outcomes

Death data was collected by the Health and Social Care information Centre (HSCIC) for English and Welsh participants, and by the Information Services Department (ISD) for Scottish participants. Death data was available up to the 15th August 2015.

7.3.5. Statistical analysis

Pearson correlation coefficients were derived for BMI, body fat distribution measures, and body composition measures. Cox proportional hazards models were used for the categorical mortality analyses for each exposure. Population and sex specific tertiles were derived for each exposure. Spline models with 4 knots were used to estimate non-linear associations between each continuous exposure and mortality. The follow-up time for the mortality risks was computed from the baseline visit date until date of death or until 15th August 2015 (for survivors). Schoenfeld residuals were used to test the proportional hazard models. Multivariate models were adjusted for age, gender, alcohol intake frequency, smoking history, and educational attainment. The Akaike Information Criterion (AIC) was obtained for each model, with lower AIC values generally indicating improved mortality model fits. Interactions between BMI, the body fat distribution measures, and body composition measures, with age (60 to 64 years and 65 to 69 years), gender, smoking history, and physical activity were evaluated. Analyses were carried out using Stata statistical software (version 14.1) and R (version 3.1.2).

7.4. Results

7.4.1. Baseline characteristics

Table 7.1 shows the baseline characteristics of the 136,933 'healthier agers' included in this analysis. Persons with a BMI <18.5 kg/m^2 were excluded from this analysis due to the high mortality risk for this group. The mean age of the male participants was 64.1 years (SD 2.8 years) and the mean age of the female participants was 63.9 years (SD 2.8 years). The proportion of never smokers relative to previous smokers was higher for the female participants (62.1%) compared to the male participants (47.4%). The mean BMI was in the Overweight range for both males (BMI 27.9 kg/m^2 SD 4.0 kg/m^2) and females (BMI 27.3 kg/m^2 SD 4.8 kg/m^2). The population and sex-specific tertiles for BMI, WC, WHR, WHtR, BF%, FMI, FFMI, and SMI are presented in **Tables 7.2** and **7.3.**

7.4.2. Associations with mortality

During the follow-up (≤8.3 years) 3,180 participants died. Using the World Health Organization categories, there was an increased risk for mortality for those within the BMI Obese range (Obese-1 HR 1.25 95% CI 1.14, 1.47, Obese-2 HR 1.42 CI 1.24, 1.64, Obese-3 HR 2.17 95% CI 1.78, 2.63) relative to those within the conventional BMI Normal range (**Table 7.4**). Those within the BMI Overweight range were not significantly different to those within the BMI Normal range for mortality.

Figure 7.1 shows the association between the tertiles of BMI and mortality with adjustments for age, sex, smoking history, alcohol intake, and education attainment, and the AIC model fit. The BMI tertile ranges can be found in **Table 7.2**. Supplementary material Table S7.1 shows the number of deaths per BMI tertile. There were increased mortality risks (HR 1.28 95% CI 1.17, 1.39) for those within the higher BMI tertiles relative to those within the lower tertile. The AIC for the BMI model was 72937.

Table 7.1 | Baseline characteristics of the 'healthier agers' aged 60 to 69 years (*n* = 136,933) from the UK Biobank

Variable	**Males (64,607)**	**Females (72,326)**
Age years, mean (SD)	64.1 (2.8)	63.9 (2.8)
BMI mean (SD)	27.9 (4.0)	27.3 (4.8)
Waist circumference mean (SD)	97.8 (10.9)	85.8 (11.9)
Waist-to-hip ratio (WHR) mean (SD)	0.94 (0.06)	0.83 (0.07)
Waist-to-height ratio (WHtR) mean (SD)	0.56 (0.06)	0.53 (0.08)
Body fat percentage mean (SD)	26.2 (5.5)	37.7 (6.2)
Fat mass index (FMI) mean (SD)	7.5 (2.6)	10.6 (3.5)
Fat free mass index (FFMI) mean (SD)	20.4 (1.8)	16.8 (1.6)
Skeletal mass index (SMI) mean (SD)	9.0 (0.9)	6.5 (0.9)
Alcohol intake frequency, n (%)		
Never	3,566 (5.5)	7,229 (10.0)
Special occasions only	4,382 (6.8)	11,074 (15.3)
One to three times a month	4,744 (7.3)	8,546 (11.8)
Once or twice a week	15,284 (23.7)	17,606 (24.3)
Three of four times a week	17,239 (26.7)	14,490 (20.0)
Daily or almost daily	19,392 (30.0)	13,381 (18.5)
Smoking status, n (%)		
Never	30,598 (47.4)	44,892 (62.1)
Previous	34,009 (52.6)	27,434 (37.9)
Education, n (%)		
None	16,000 (24.8)	19,507 (27.0)
CSEs	884 (1.4)	1,610 (2.2)
GCSEs/O-levels	6,604 (10.2)	12,987 (18.0)
A-levels/NVQ/HND/HNC	11,691 (18.1)	8,683 (12.0)
Professional Qualification	9,737 (15.1)	12,129 (16.8)
College of University degree	19,691 (30.5)	17,410 (24.1)
Diagnosed disease at baseline, n (%)		
Coronary Heart Disease	7,541 (11.7)	3,432 (4.8)
Type 2 Diabetes	5,322 (8.2)	2,957 (4.1)
Follow-up years, mean (SD)	6.4 (0.9)	6.5 (0.9)

Note: 'Healthier agers' were non-smokers without recent cancer (except non-melanoma skin cancer), dementia, or heart failure and survived the first 1.9 years. Persons with a BMI <18.5 kg/m^2 were excluded. WHR: waist-to-hip, WHtR: waist-to-height, FMI: fat mass index, FFMI: fat free mass index, SMI: skeletal mass index.

Table 7.2 | Cut off values for each tertile (lower, intermediate, higher) for BMI and body fat distribution measures for male and female 'healthier agers' aged 60 to 69 years (*n* = 136,933) from the UK Biobank

Sex	BMI	WC	WHR	WHtR
Males				
Lower	18.56-25.91	60.0-93.0	0.59-0.92	0.34-0.53
Intermediate	>25.91-28.97	>93.0-101.0	>0.92-0.97	>0.53-0.58
Higher	>28.97	>101.1	>0.97	>0.58
Females				
Lower	18.50-24.81	52.0-80.0	0.50-0.79	0.35-0.49
Intermediate	>24.81-28.56	>80.0-90.0	>0.79-0.85	>0.49-0.56
Higher	>28.56	>90.1	>0.85	>0.56

Note: 'Healthier agers' were non-smokers without recent cancer (except non-melanoma skin cancer), dementia, heart failure and survived the first 1.9 years. Persons with a BMI <18.5 kg/m^2 were excluded. WC: waist circumference, WHR: waist-to-hip ratio, WHtR: waist-to-height ratio.

Table 7.3 | Cut off values for each tertile (lower, intermediate, higher) for body composition measures for male and female 'healthier agers' aged 60 to 69 years (*n* = 136,933) from the UK Biobank

Sex	BF%	FMI	FFMI	SMI
Males				
Lower	6.9-24.0	1.46-6.26	13.58-19.52	5.53-8.65
Intermediate	>24.0-28.6	>6.26-8.20	>19.52-21.00	>8.65-9.33
Higher	>28.6	>8.20	>21.00	>9.33
Females				
Lower	10.7-35.1	2.03-8.74	11.39-15.98	4.18-6.10
Intermediate	>35.1-40.5	>8.74-11.52	>15.98-17.25	>6.10-6.67
Higher	>40.5	>11.52	>17.25	>6.67

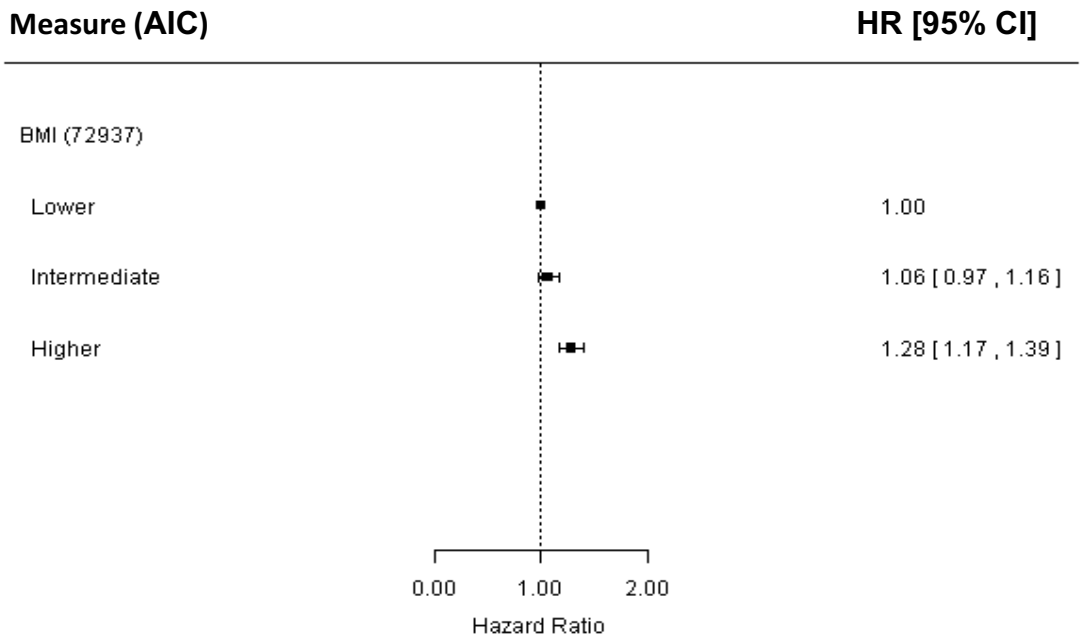
Note: 'Healthier agers' were non-smokers without recent cancer (except non-melanoma skin cancer), dementia, heart failure and survived the first 1.9 years. Persons with a BMI <18.5 kg/m^2 were excluded
BF%: body fat percentage, FMI: fat mass index, FFMI: fat free mass index, SMI: skeletal mass index.

Table 7.4 | Hazard ratios for mortality by BMI category 'healthier agers' aged 60 to 69 years (*n* = 136,933) from the UK Biobank

BMI Category	HR (95% CI)
Normal weight 18.5 to <25.0	1.00
Overweight 25.0 to <30.0	1.08 (0.99, 1.17)
Obese-1 30.0 to <35.0	1.25 (1.14, 1.37)
Obese-2 35.0 to <40.0	1.42 (1.24, 1.64)
Obese-3 ≥40.0	2.17 (1.78, 2.63)

Note: 'Healthier agers' were non-smokers without recent cancer (except non-melanoma skin cancer), dementia, or heart failure and survived the first 1.9 years. Persons with a BMI <18.5 kg/m^2 were excluded.

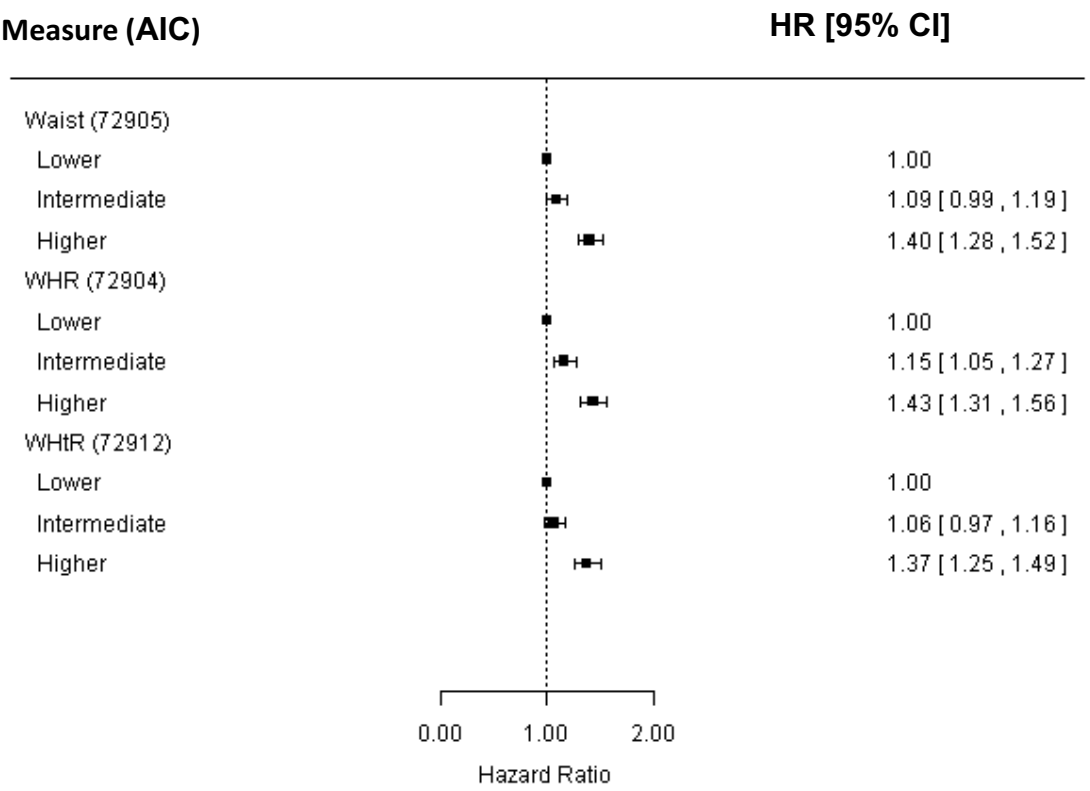
Figure 7.1 | Association of BMI tertiles with mortality and the AIC model fit for 'healthier agers' aged 60 to 69 years (*n* =136,933) from the UK Biobank



Note: 'Healthier agers' were non-smokers without recent cancer (except non-melanoma skin cancer), dementia, heart failure and survived the first 1.9 years. Cox proportional hazards models were adjusted for age, sex, alcohol intake, smoking history, and education. BMI tertiles were population and sex specific. For males, the BMI tertiles were lower 18.56-25.91, intermediate >25.91-28.97, and higher >28.97kg/m^2. For females, the BMI tertiles were lower 18.50-24.81, intermediate >24.81-28.56, and higher >28.56 kg/m^2. Persons with a BMI <18.5 kg/m^2 were excluded.

The body fat distribution measures were divided into population and sex specific tertiles. An overview of the WC, WHR, and WHtR tertiles can be found in **Table 7.2**. Supplementary material Table S7.1 shows the number of deaths per WC, WHR and WHtR tertile. **Figure 7.2** displays the association between tertiles of WC, WHR, and WHtR and mortality, and the AIC model fit. There was an increased mortality risk for those within the higher tertile of WC (HR 1.40 CI 1.28, 1.52), WHR (HR 1.43 CI 1.31, 1.56), and WHtR (HR 1.37 CI 1.25, 1.49) relative to those within the lower tertiles of each measure. All three models showed a substantial improvement in the mortality model fit relative to the BMI model. The lowest AIC value was achieved for the WHR model; however, all the body fat distribution measures were comparable (AIC values within 10).

Figure 7.2 | Association of WC, WHR, and WHtR tertiles with mortality and the AIC model fit for 'healthier agers' aged 60 to 69 years (*n* = 136,933) from the UK Biobank

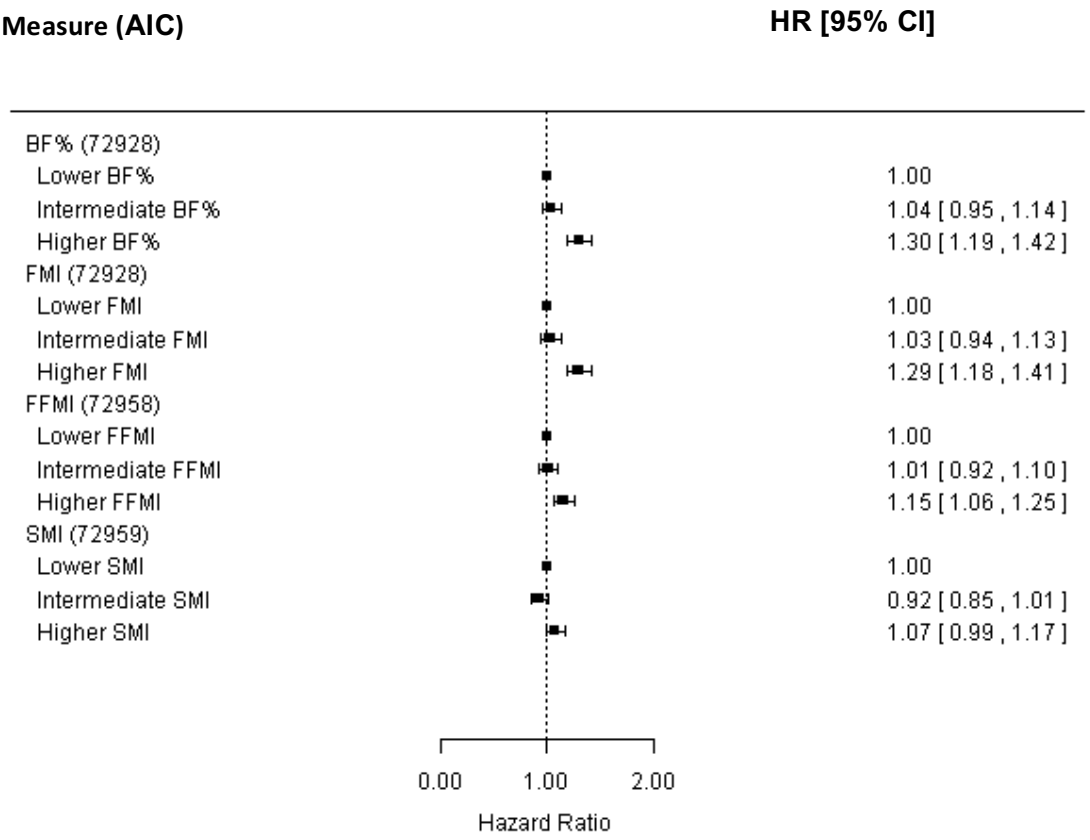


Note: 'Healthier agers' were non-smokers without recent cancer (except non-melanoma skin cancer), dementia, heart failure and survived the first 1.9 years. Cox proportional hazards models were adjusted for age, sex, alcohol intake, smoking history, and education. Waist circumference, WHR, and WHtR tertiles were population and sex specific. For males, the tertiles for waist circumference were lower 60.0-93.0, intermediate >93.0-101.0, and higher >101.1 cm. For females, the tertiles for waist circumference were lower 52.0- 80.0, intermediate >80.0-90.0, and higher >90.1cm. For males, the tertiles for WHR were lower 0.59-0.92, intermediate >0.92- 0.97, and higher >0.97. For females, the tertiles for WHR were lower 0.50-0.79, intermediate >0.79-0.85, and higher >0.85. For males, the tertiles for WHtR were lower 0.34-0.53, intermediate >0.53-0.58, and higher >0.58. For females, the tertiles for WHtR were lower 0.35-0.49, intermediate >0.49-0.56, and higher >0.56. WHR: waist-to-hip ratio, WHtR: waist-to-height ratio. Persons with a BMI <18.5 kg/m^2 were excluded.

The body composition measures (BF%, FMI, FFMI, and SMI) were divided into population and sex specific tertiles with the corresponding ranges presented in **Table 7.3**. Supplementary Table S7.1 shows the number of deaths per BF%, FMI, FFMI and SMI tertiles. **Figure 7.3** displays the association between tertiles of BF%, FMI, FFMI, and SMI with mortality and the AIC model fit. There was an increased mortality risk for those within the higher tertile of body fat percentage (HR 1.30 CI 1.19, 1.42), FMI (HR 1.29 CI 1.18, 1.41), and FFMI (HR 1.15, CI 1.06, 1.25) relative to those within the lower tertiles of each measure. There were no significant mortality associations for the tertiles of SMI. The mortality model fit using models containing body fat percentage or FFMI were comparable to the BMI model (AIC values within 10 units). The mortality model fit using FFMI and SMI showed no improvement compared to the model containing BMI.

A further analysis was conducted for the SMI tertiles after adjusting for the WHO BMI categories. This was due to a positive association between BMI and SMI (**Table 7.5**). This, analysis revealed there was a reduced mortality risk for those within the intermediate and higher SMI tertiles compared to those within the lower SMI tertile. The AIC was 72907, which was comparable to the model fits for WC, WHR, and WHtR.

Figure 7.3 | Association of BF%, FMI, FFMI, and SMI tertiles with mortality and the AIC model fit for 'healthier agers' aged 60 to 69 years (*n* =136,933) from the UK Biobank



Note: 'Healthier agers' were non-smokers without recent cancer (except non-melanoma skin cancer), dementia, heart failure and survived the first 1.9 years. Cox proportional hazards models were adjusted for age, sex, alcohol intake, smoking history, and education. BF %, FMI, FFMI and SMI tertiles were population and sex specific. For males, the BF % tertiles were lower 6.9-24.0, intermediate >24.0-28.6, and higher >28.6%. For females, the BF % tertiles were lower 10.7-35.1, intermediate >35.1-40.5, and higher >40.5%. For males, the FMI tertiles were lower 1.46-6.26, intermediate >6.26-8.20, and higher >8.20. For females, the FMI tertiles were lower 2.03-8.74, intermediate >8.74-11.52, and higher >11.52. For males, the FFMI tertiles were lower 13.58-19.52, intermediate >19.52-21.00, and higher >21.00. For females, the FFMI tertiles were lower 11.39-15.98, intermediate >15.98-17.25, and higher >17.25. For males, the SMI tertiles were lower 5.53-8.65, intermediate >8.65- 9.33, and higher >9.33. For females, the SMI tertiles were lower 4.18-6.10, intermediate >6.10-6.67, and higher >6.67. BF %: body fat percentage, FMI: fat mass index, FFMI: fat free mass index, SMI: skeletal mass index. *Persons with a BMI <18.5 kg/m^2 were excluded.*

Table 7.5 | Hazard ratios for mortality by SMI tertiles with adjustment for BMI for 'healthier agers' aged 60 to 69 years (*n* = 136,933) from the UK Biobank

SMI tertiles adjusted for BMI category	**HR (95% CI)**
Lower SMI tertile	1.00
Intermediate SMI tertile	0.87 (0.79, 0.95)
Higher SMI tertile	0.89 (0.80, 0.98)

Note: 'Healthier agers' were non-smokers without recent cancer (except non-melanoma skin cancer), dementia, heart failure and survived the first 1.9 years. Cox proportional hazards models were adjusted for age, sex, alcohol intake, smoking history, and education. SMI tertiles were population and sex specific. For males, the SMI tertiles were lower 5.53-8.65, intermediate >8.65- 9.33, and higher >9.33. For females, the SMI tertiles were lower 4.18-6.10, intermediate >6.10-6.67, and higher >6.67. SMI: skeletal mass index. Persons with a BMI <18.5 kg/m^2 were excluded. BMI was categorised according to the World Health Organization.

7.4.3. Interactions

There were no significant interactions between gender, age (60 to 64 years and 65 to 69 years), or physical activity (data available for *n* = 125,873) and BMI, the body fat distribution measures, or body composition measures. There was a significant interaction between SMI tertiles and smoking history. **Table 7.6** shows the hazard ratios for mortality stratified by smoking history. The mortality risk for those within the higher SMI tertile was increased for never smokers, and not significantly different for former smokers, relative to those within the lower tertile for never smokers and former smokers, respectively. The mortality risk for those within the intermediate SMI tertile was not significantly different for never smokers, whereas there was a reduced risk for former smokers relative to those within the lower tertile for never smokers and former smokers, respectively.

Table 7.6 | Hazard ratios (95% CI) for mortality by SMI tertiles for 'healthier agers' aged 60 to 69 years (*n* =136,933) stratified by smoking history using the UK Biobank

SMI tertiles	**Never smokers** [a]	**Former smokers** [a]
Lower SMI tertile	458/25999	621/19648
	1.00	1.00
Intermediate SMI tertile	454/25144	510/20503
	1.07 (0.94 to 1.22)	0.82 (0.73 to 0.92)
Higher SMI tertile	484/24347	653/21292
	1.19 (1.05 to 1.36)	0.99 (0.89 to 1.11)

[a] Cell contents: events/number, HR (95% CI)

Note: 'Healthier agers' were non-smokers without recent cancer (except non-melanoma skin cancer), dementia, heart failure and survived the first 1.9 years. Cox proportional hazards models were adjusted for age, sex, alcohol intake, smoking history, and education. SMI tertiles were population and sex specific. For males, the SMI tertiles were lower 5.53-8.65, intermediate >8.65- 9.33, and higher >9.33. For females, the SMI tertiles were lower 4.18-6.10, intermediate >6.10-6.67, and higher >6.67. SMI: skeletal mass index. Persons with a BMI <18.5 kg/m^2 were excluded.

7.4.4. Adjustment for physical activity

Mortality risk estimates were little changed with further adjustment for physical activity where available (**Table 7.5 and 7.6**).

Table 7.7 | Hazard ratios (95% CI) for mortality by BMI and body fat distribution tertiles for 'healthier agers' aged 60 to 69 years with further adjustment for physical activity using the UK Biobank (*n* = 125,873)

Tertiles	BMI	WC	WHR	WHtR
Lower	1.00	1.00	1.00	1.00
Intermediate	1.08 (0.98, 1.18)	1.09 (0.99, 1.19)	1.15 (1.05, 1.27)	1.06 (0.96, 1.16)
Higher	1.26 (1.15, 1.38)	1.38 (1.26, 1.51)	1.40 (1.27, 1.53)	1.34 (1.22, 1.48)

Note: 'Healthier agers' were non-smokers without recent cancer (except non-melanoma skin cancer), dementia, heart failure and survived the first 1.9 years. Persons with a BMI <18.5 kg/m^2 were excluded WC: waist circumference, WHR: waist-to-hip ratio, WHtR: waist-to-height ratio

Table 7.8 | Hazard ratios (95% CI) for mortality by body composition tertiles for 'healthier agers' aged 60 to 69 years with further adjustment for physical activity using the UK Biobank (*n* = 125,873)

	BF%	FMI	FFMI	SMI
Lower	1.00	1.00	1.00	1.00
Intermediate	1.02 (0.93, 1.12)	1.03 (0.94, 1.14)	1.01 (0.92, 1.11)	0.95 (0.86, 1.04)
Higher	1.28 (1.16, 1.41)	1.27 (1.16, 1.40)	1.15 (1.05, 1.26)	1.08 (0.99, 1.18)

Note: 'Healthier agers' were non-smokers without recent cancer (except non-melanoma skin cancer), dementia, heart failure and survived the first 1.9 years. Persons with a BMI <18.5 kg/m^{2}were excluded. BF%: body fat percentage, FMI: fat mass index, FFMI: fat free mass index, SMI: skeletal mass index.

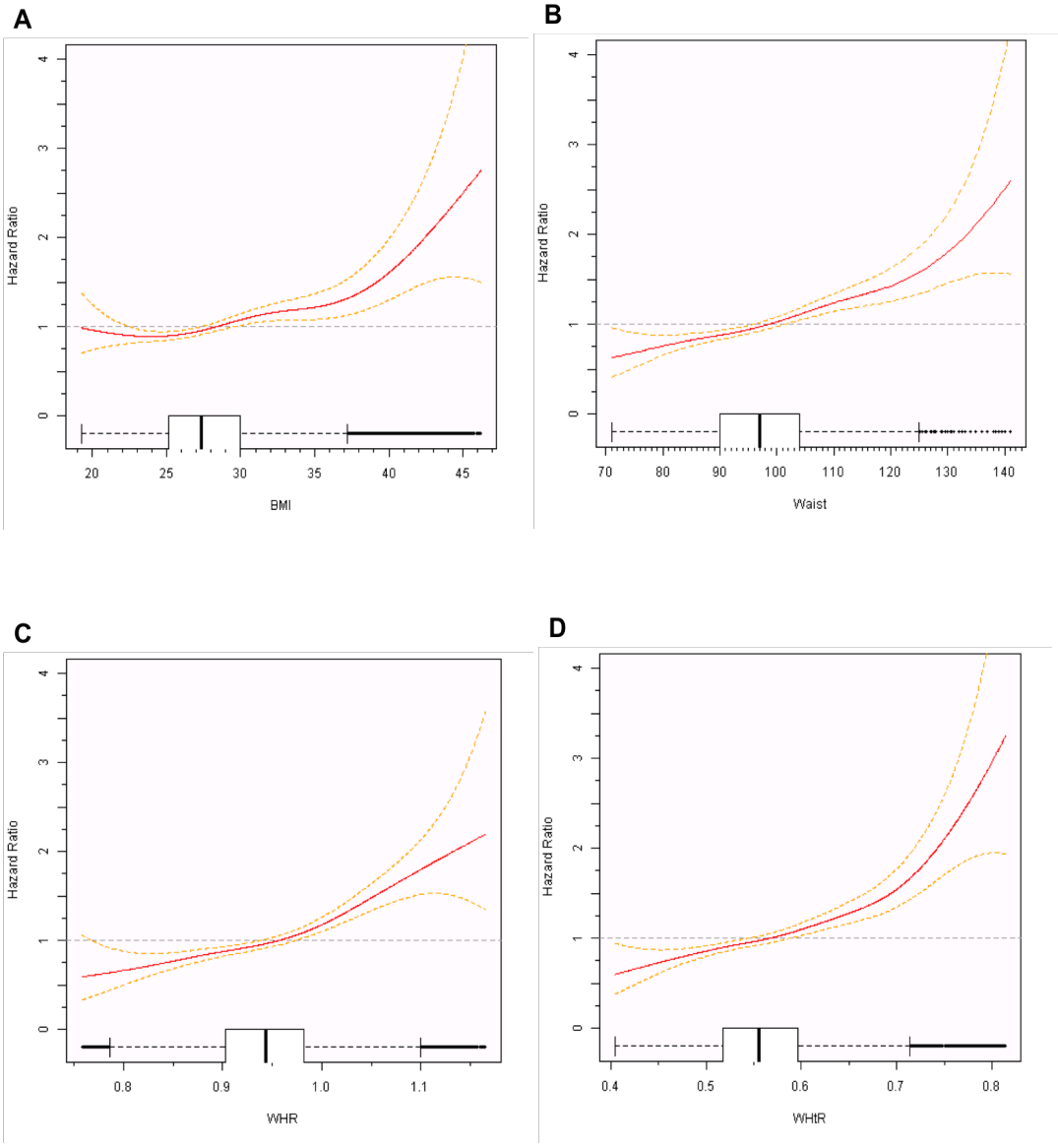
7.4.5. Continuous measures

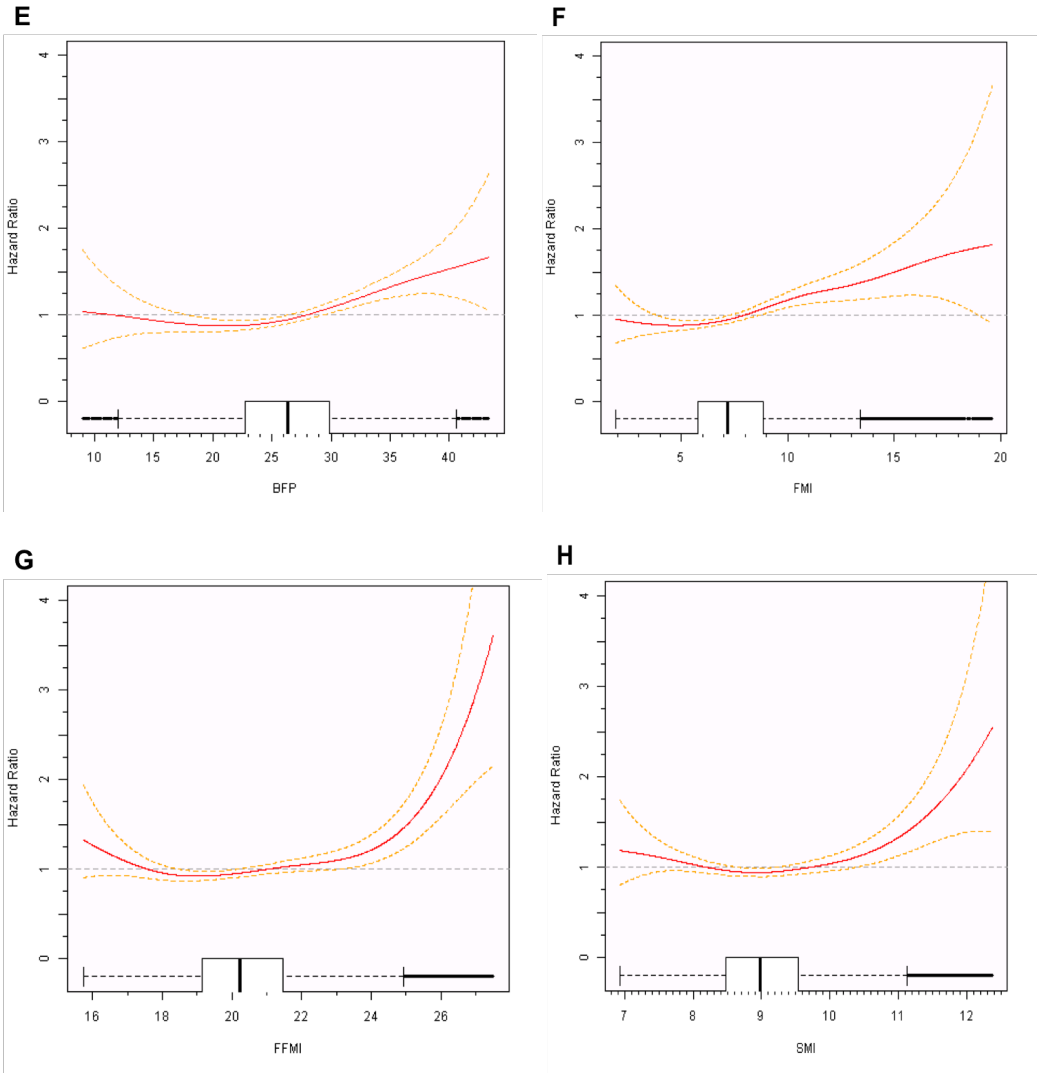
The associations between the continuous measures of BMI, WC, WHR, WHtR, BF%, FMI, FFMI, SMI and mortality were estimated. **Figures 7.4** and **7.5** show these associations for males and females separately. For males, there were positive associations with mortality for BMI, WC, WHR, WHtR, and FMI. For males ≥25th percentile of BF%, there was also a positive association. A similar pattern presented for the females with an attenuation of the mortality risks and gradients for these measures. There was no association between FFMI and SMI, apart from extreme upper values showing an increased mortality risk for the males. There was also no association between FFMI and SMI and mortality was for the females.

7.4.6. Correlations between measures

Correlations between BMI, measures of body fat distribution and body composition are presented in **Table 7.9** (see supplementary material figures S7.1 and S7.2 for the correlations between BMI and the other measures). There were strong correlations between BMI and WC, WHtR, FMI, FFMI, and body fat percentage (for males this ranged from 0.79 to 0.93; females this ranged from 0.84 to 0.97). Modest correlations were found between BMI and WHR (males 0.59; females 0.44), and SMI (males 0.62; females 0.49). SMI exhibited modest to weak correlations with all variables except FFMI in males (0.89).

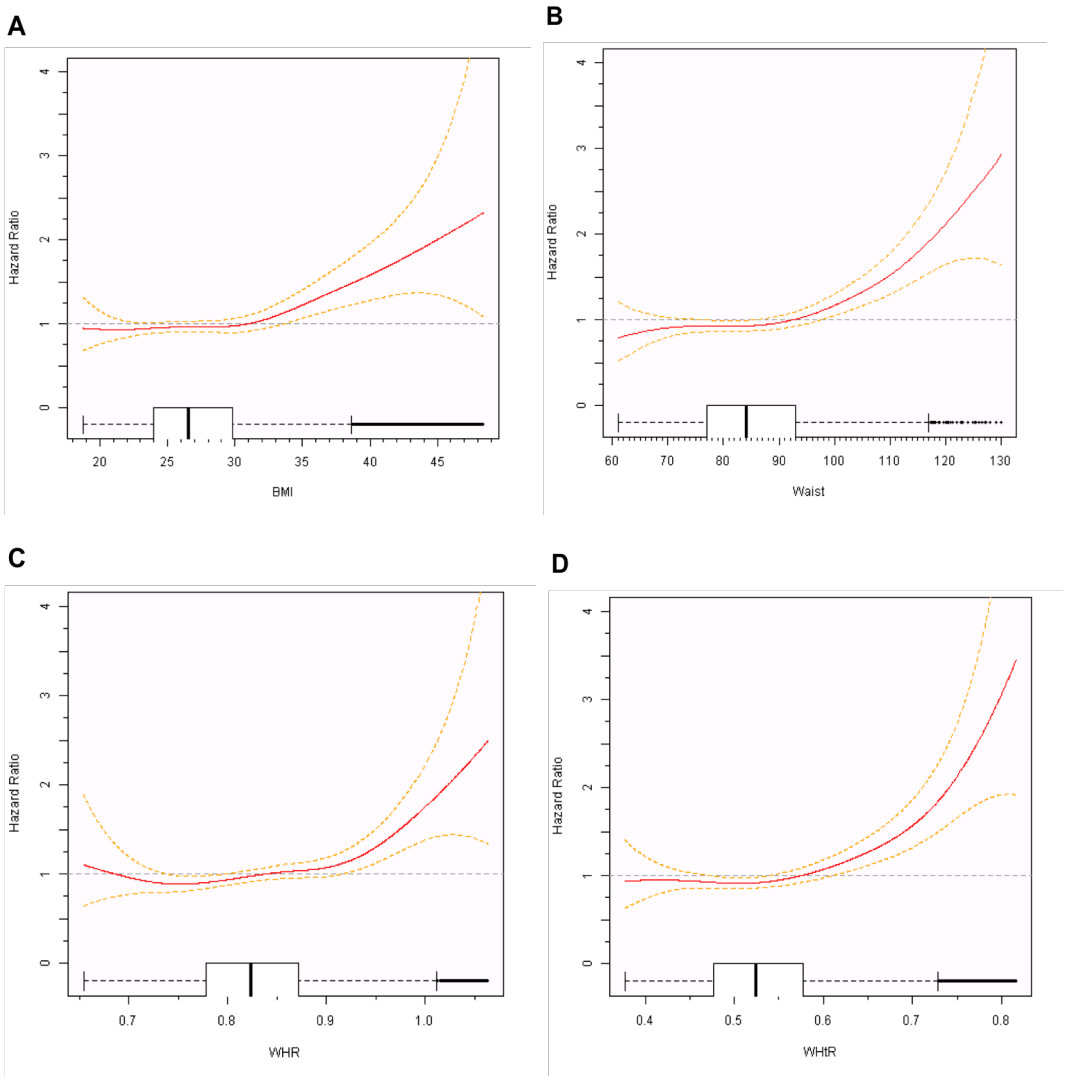
Figure 7.4 | Spline point estimates for male 'healthier agers' aged 60 to 69 years (*n* = 64,607) from the UK Biobank for BMI (A), WC (B), WHR (C), WHtR (D), BF% (E), FMI (F), FFMI (G), and SMI (H)

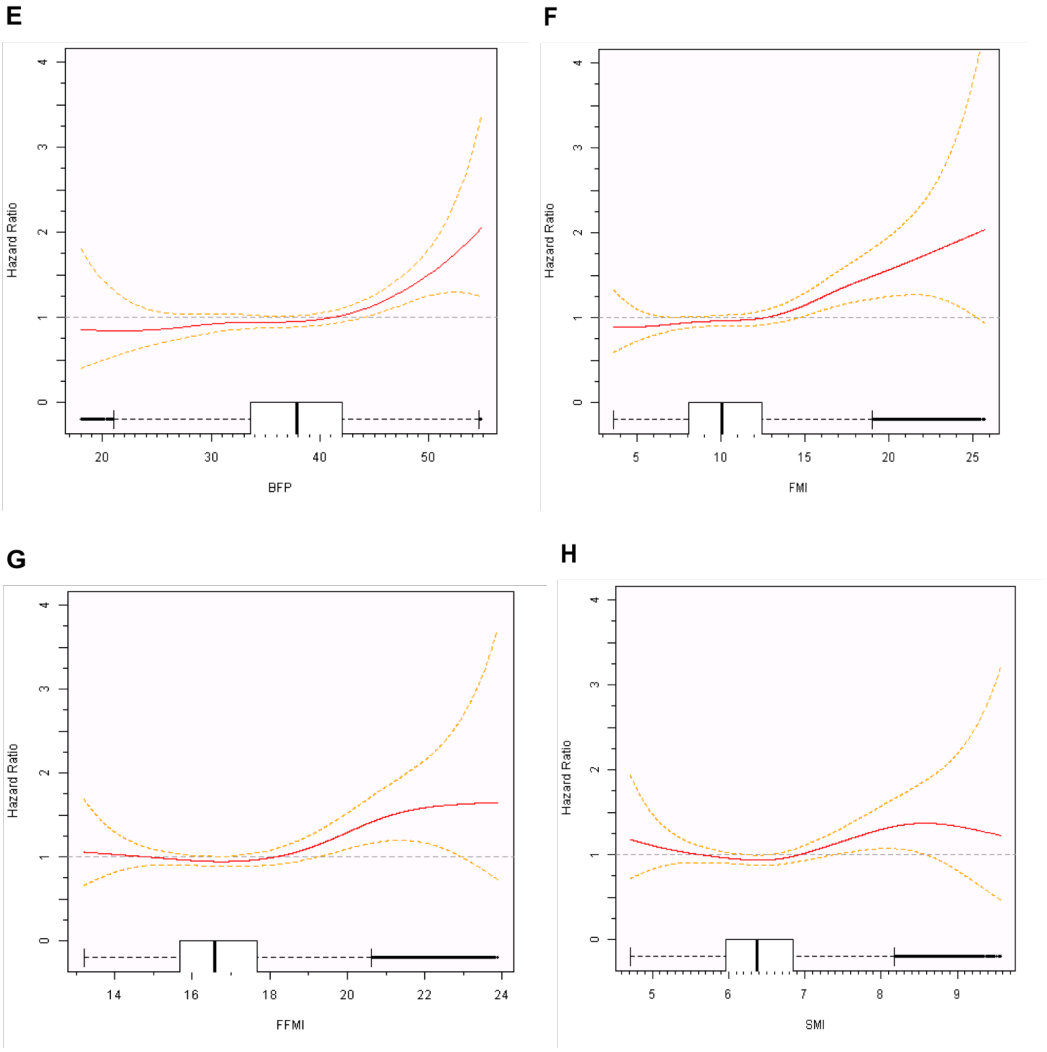




Note: 'Healthier agers' were non-smokers without recent cancer (except non-melanoma skin cancer), dementia, heart failure and survived the first 1.9 years. Models were adjusted for age, sex, alcohol intake, smoking history, and education WC: waist circumference, WHR: waist-to-hip ratio; WHtR: waist-to-height ratio; BF%: body fat percentage; FMI: fat mass index; FFMI: fat free mass index; SMI: skeletal mass index. Persons with a BMI <18.5 kg/m^2 were excluded.

Figure 7.5 | Spline point estimates for female 'healthier agers' aged 60 to 69 years (*n* = 72,326) from the UK Biobank for BMI (A), WC (B), WHR (C), WHtR (D), BF% (E), FMI (F), FFMI (G), and SMI (H)





Note: 'Healthier agers' were non-smokers without recent cancer (except non-melanoma skin cancer), dementia, heart failure and survived the first 1.9 years. Models were adjusted for age, sex, alcohol intake, smoking history, and education WC: waist circumference, WHR: waist-to-hip ratio; WHtR: waist-to-height ratio; BF%: body fat percentage; FMI: fat mass index; FFMI: fat free mass index; SMI: skeletal mass index. Persons with a BMI <18.5 kg/m^2 were excluded.

Table 7.9 | Pearson's Correlation coefficients between BMI, fat distribution measures, and body composition measures for male 'Healthier agers' aged 60 to 69 years from the UK Biobank

	BMI	WC	WHR	WHtR	FMI	FFMI	BF%	SMI
BMI	1.00							
WC	0.87	1.00						
WHR	0.59	0.79	1.00					
WHtR	0.89	0.94	0.80	1.00				
FMI	0.93	0.86	0.61	0.88	1.00			
FFMI	0.87	0.70	0.44	0.70	0.63	1.00		
BF%	0.79	0.77	0.60	0.80	0.95	0.40	1.00	
SMI	0.62	0.43	0.25	0.46	0.33	0.89	0.08	1.00

Note: 'Healthier agers' were non-smokers without recent cancer (except non-melanoma skin cancer), dementia, heart failure and survived the first 1.9 years. WC: waist circumference, WHR: waist-to-hip ratio, WHtR: waist-to-height ratio, BF%: body fat percentage, FMI: fat mass index, FFMI: fat free mass index, SMI: skeletal mass index. Persons with a BMI <18.5 kg/m^2 were excluded.

Table 7.10 | Pearson's Correlation coefficients between BMI, fat distribution measures, and body composition measures for female 'Healthier agers' aged 60 to 69 years from the UK Biobank

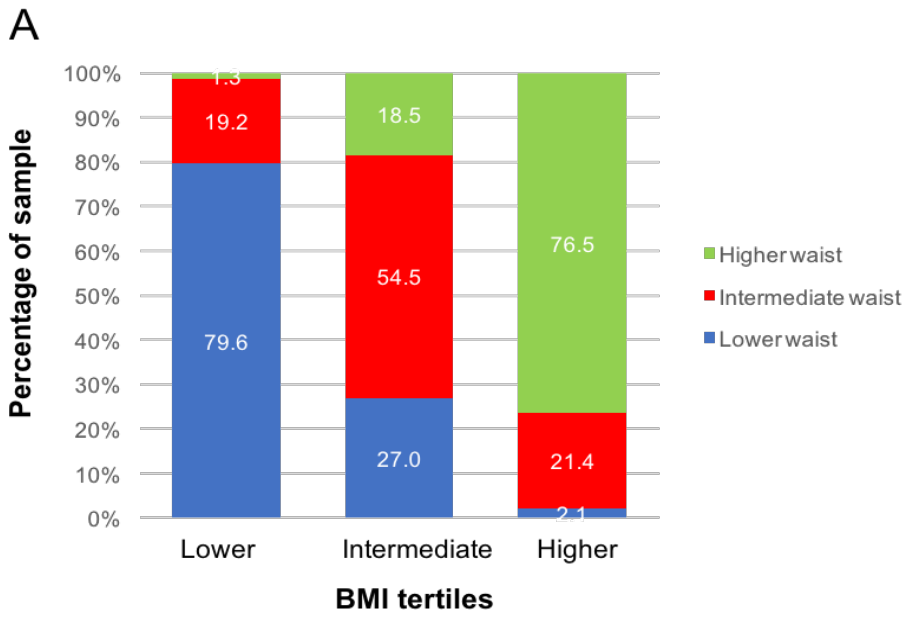
	BMI	Waist	WHR	WHtR	FMI	FFMI	BF%	SMI
BMI	1.00							
Waist	0.86	1.00						
WHR	0.44	0.74	1.00					
WHtR	0.88	0.96	0.74	1.00				
FMI	0.97	0.86	0.43	0.86	1.00			
FFMI	0.85	0.68	0.35	0.73	0.70	1.00		
BF%	0.84	0.79	0.42	0.77	0.93	0.45	1.00	
SMI	0.49	0.38	0.19	0.39	0.35	0.69	0.15	1.00

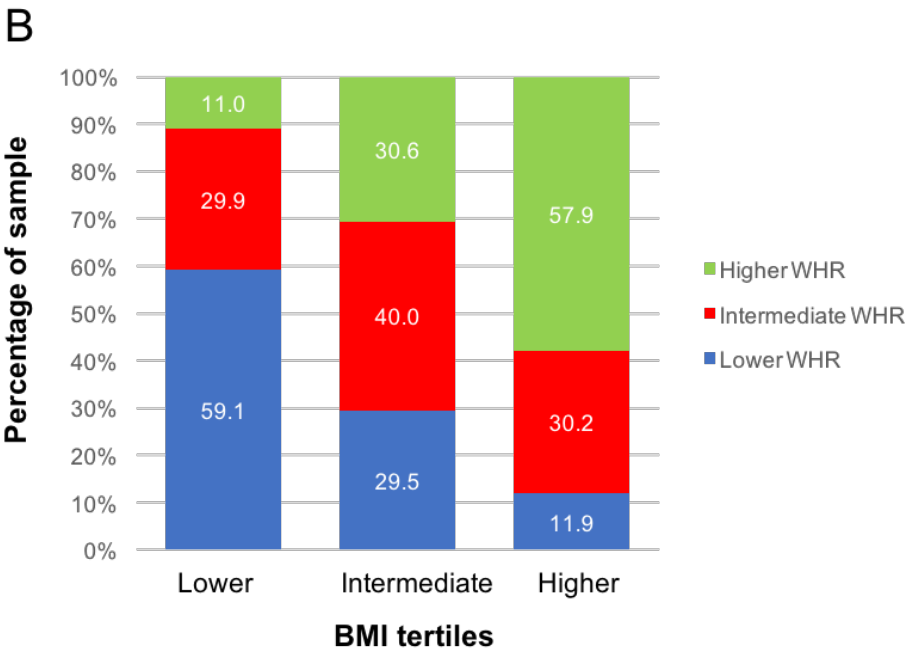
Note: 'Healthier agers' were non-smokers without recent cancer (except non-melanoma skin cancer), dementia, heart failure and survived the first 1.9 years. WHR: waist-to-hip ratio, WHtR: waist-to-height ratio, BF%: body fat percentage, FMI: fat mass index, FFMI: fat free mass index, SMI: skeletal mass index. Persons with a BMI <18.5 kg/m^2 were excluded.

7.4.7. Concordance agreement between tertile measures

Figure 7.6 (A to G) shows the concordance between tertiles of BMI with tertiles of WC, WHR, WHtR, BF%, FMI, FFMI, and SMI (see **Tables 7.2** and **7.3** for the tertile ranges). Concordance refers to persons being within the same tertile measure for each comparison, for example in both BMI lower tertile and WHtR lower tertile. Overall, the highest concordance was found between BMI tertiles and the FMI tertiles. Specifically, for the lower BMI tertile the lowest concordance was found for the SMI lower tertile (58.8%). For the intermediate and higher BMI tertiles the lowest concordance was found for the WHR intermediate and higher tertiles, respectively (40.0% for the intermediate tertile and 57.9% for the higher tertile). For most measures, there was high concordance for those within the lower and higher tertiles of BMI and the corresponding lower/higher tertiles of the other measures, respectively. The concordance of the other measures varied within the intermediate BMI tertile, except for FMI which showed high concordance.

Figure 7.6 | Concordance between BMI tertiles and WC (A), WHR (B), WHtR (C), BF% (D), FMI (E), FFMI (F) and SMI (G) tertiles for 'healthier agers' aged 60 to 69 years (*n* = 136,933) from the UK Biobank





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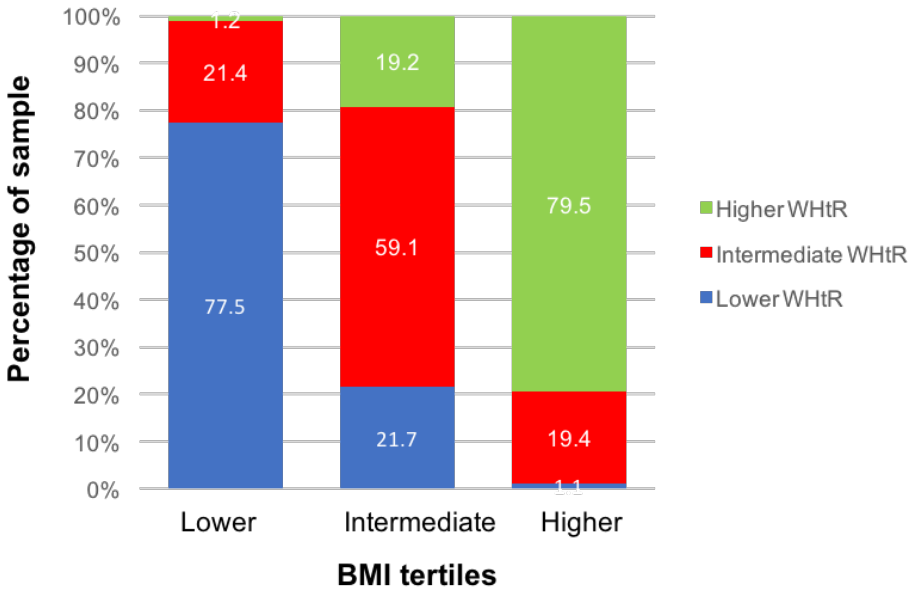
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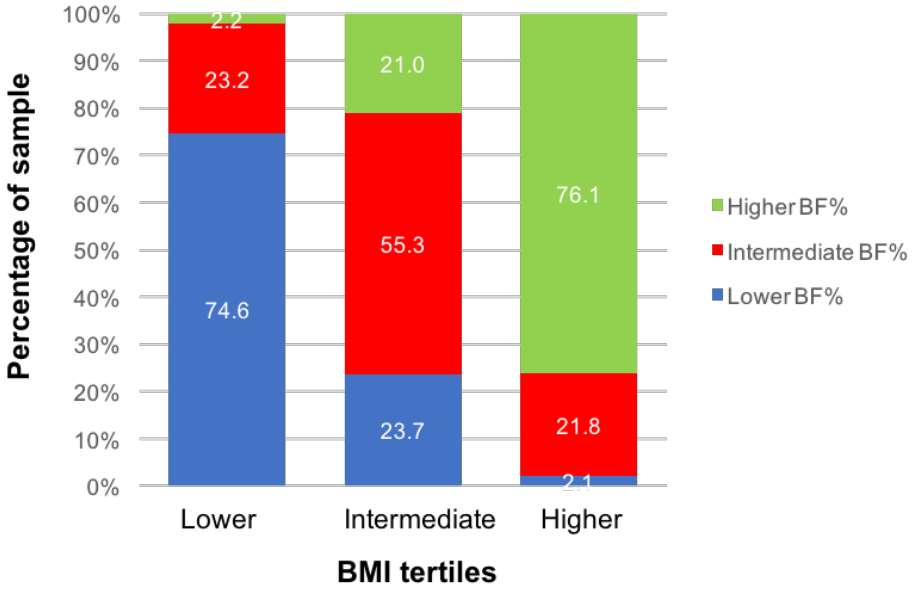
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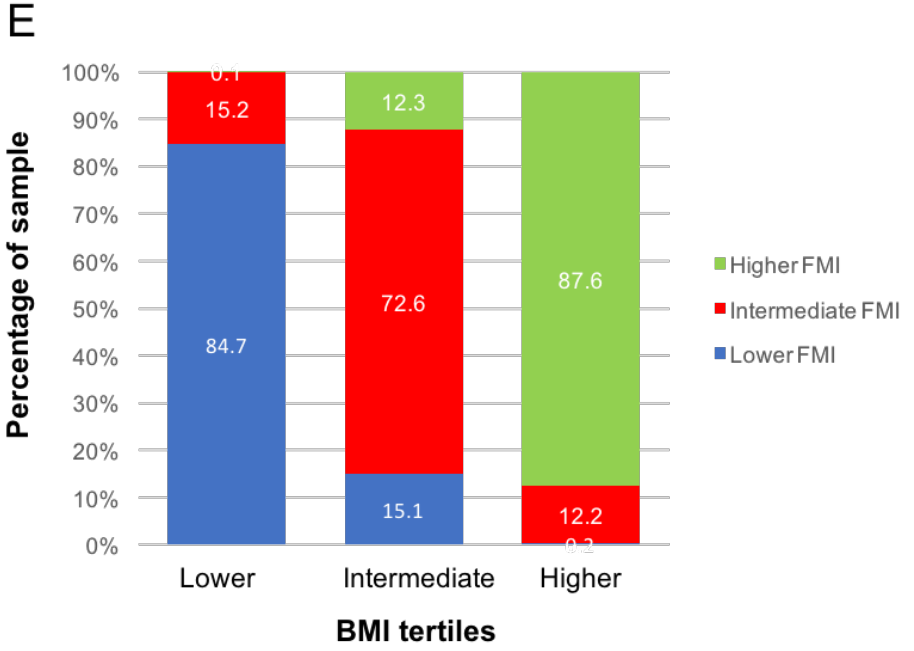
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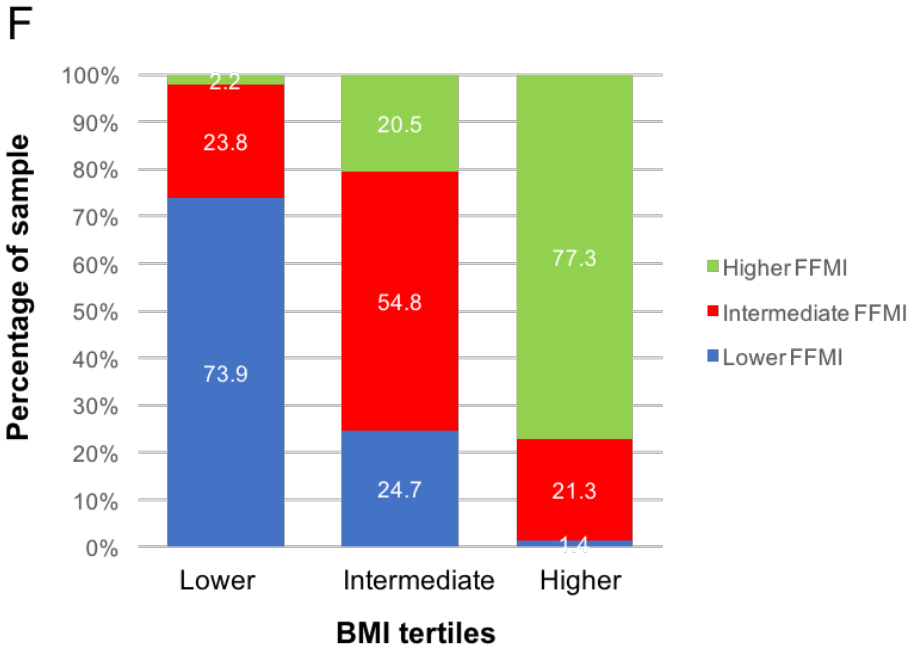
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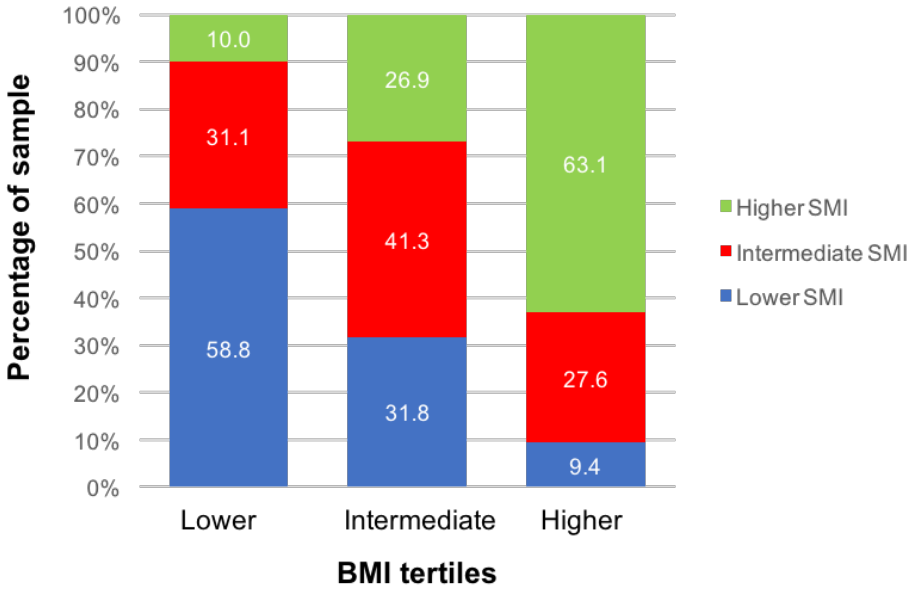


Note: 'Healthier agers' were non-smokers without recent cancer (except non-melanoma skin cancer), dementia, heart failure & survived the first 1.9 years. Population & sex specific tertiles were derived for each measure. For males, the BMI tertiles were lower 18.56-25.91, intermediate >25.91-28.97 & higher >28.97. For females, the BMI tertiles were lower 18.50-24.81, intermediate >24.81-28.56 & higher >28.56 kg/m^2. For males, the tertiles for waist circumference were lower 60.0-93.0, intermediate >93.0-101.0 & higher >101.1 cm. For females, the tertiles for waist circumference were lower 52.0-80.0, intermediate >80.0-90.0 & higher >90.1cm. For males, the tertiles for WHR were lower 0.59-0.92, intermediate >0.92-0.97 & higher >0.97. For females, the tertiles for WHR were lower 0.50-0.79, intermediate >0.79-0.85 & higher >0.85. For males, the tertiles for WHtR were lower 0.34-0.53, intermediate >0.53-0.58 & higher >0.58. For females, the tertiles for WHtR were lower 0.35-0.49, intermediate >0.49-0.56 & higher >0.56. For males, the BF % tertiles were lower 6.9-24.0, intermediate >24.0-28.6 & higher >28.6%. For females, the BF % tertiles were lower 10.7-35.1, intermediate >35.1-40.5 & higher >40.5%. For males, the FMI tertiles were lower 1.46-6.26, intermediate >6.26-8.20 & higher >8.20. For females, the FMI tertiles were lower 2.03-8.74, intermediate >8.74-11.52 & higher >11.52. For males, the FFMI tertiles were lower 13.58-19.52, intermediate >19.52-21.00 & higher >21.00. For females, the FFMI tertiles were lower 11.39-15.98, intermediate >15.98-17.25 & higher >17.25. For males, the SMI tertiles were lower 5.53-8.65, intermediate >8.65-9.33 & higher >9.33. For females, the SMI tertiles were lower 4.18-6.10, intermediate >6.10-6.67 & higher >6.67. WHR: waist-to-hip ratio, WHtR: waist-to-height ratio, BF %: body fat percentage, FMI: fat mass index, FFMI: fat free mass index, SMI: skeletal mass index. Persons with a BMI <18.5 kg/m^2 were excluded.

7.5. Discussion

I aimed to compare established measures of body fat distribution and body composition to BMI for mortality prediction for 'healthier agers' within the seventh decade of life and to describe the concordance between categories of BMI and these alternative measures. The findings I presented in this chapter showed that the mortality model fit was substantially improved when tertile measures of body fat distribution (WC, WHR, WHtR) were used compared to a model using BMI tertiles. The lowest AIC value was achieved for the model containing WHR tertiles. Overall, the results showed that 'healthier agers', after excluding underweight participants, within the higher tertile of adiposity whether measured overall or centrally were at increased risks of mortality relative to those within the lower tertiles. No significant associations were found for tertiles of SMI. However, after accounting for BMI, there were reduced mortality risks for those within the intermediate and higher tertiles of SMI compared to the lower tertile. Modest correlations were found between BMI and WHR, and SMI. The concordance (i.e. a person being in both the BMI lower tertile and WHtR lower tertile) was high between BMI tertiles and FMI tertiles. The lowest concordance was found between BMI tertiles and WHR tertiles for those within the intermediate or higher tertiles. The lowest concordance for the lower BMI tertile out of all the measures was with the SMI tertiles. The intermediate tertile of BMI, which corresponded to values within the BMI Overweight range, showed that the proportions of the different measures were variable.

7.5.1. Comparison to Chapter 4

In **Chapter 4** I showed for 'healthier agers' aged 60 to 64 years and 65 to 69 years there were increased mortality risks for those within the BMI Obese ranges relative to those within the conventional BMI Normal range using electronic health records. In this chapter, I also confirmed for 'healthier agers' aged 60 to 69 years from a large volunteer cohort that there were increased mortality risks for those within the BMI Obese ranges compared to those within the conventional BMI Normal range for those aged 60 to 69 years. The point estimates derived from the 60 to 64 year olds from the electronic health records were larger for the BMI Obese-2 and Obese-3 ranges, however, the confidence intervals overlap between the two datasets. In **Chapter 4** I showed that the mortality risks were not statistically different for those within the BMI

Overweight range compared to those within the BMI Normal range. In this chapter I also document that those within the BMI Overweight range are not significantly different to those within the BMI Normal range.

7.5.2. Comparison to Chapter 5

In **Chapter 5** I showed that there were elevated mortality risks for those within the lower end of the conventional BMI Normal range for all age groups. The analysis presented in this chapter did not find a substantial excess mortality for those within the lower end of the conventional BMI Normal range, as shown in the continuous BMI association with mortality. This may be due to the use of a volunteer cohort study and the different age composition.

7.5.3. Comparison to previous literature

The results presented in this chapter for the tertiles of WC and WHR tertiles contrast with a previous analysis which also divided the body fat distribution measures into tertiles. Batsis, *et al*., (2014) reported the mortality risks for those within the higher tertiles of WC or WHR were not significantly different to those within the lower tertiles for adults aged ≥60 years (excluding current smokers and those with heart failure, cancer, kidney disease, or respiratory disease) enrolled in NHANES III during a mean follow-up period of 11.8 years (Batsis, Singh and Lopez-Jimenez, 2014). This could be due to the different cut points for the body fat distribution measures, exclusions, model adjustments, and the different age composition. The NHANES III study used a much broader age range. Inclusion of the youngest and oldest old may have distorted the mortality risks for the NHANES III study (**Chapter 1**). Similarly, the results presented in this chapter for body fat percentage are also in discordance to those presented by Batsis, *et al*., (2014) where non-significant mortality risks were presented.

Previous analyses have shown non-significant mortality risks (Baik *et al.*, 2000; Wannamethee *et al.*, 2007), or reduced mortality risks (Reis *et al.*, 2009) for measures of central adiposity. Reduced mortality risks for women within the middle distribution of body fat percentage has also been documented (Dolan *et al.*, 2007; Bea *et al.*, 2015) which was not observed in this chapter. However, there are challenges

comparing my results with prior analyses due to differing categories of body fat distribution and body composition measures, age composition, and exclusions.

7.5.4. Strengths and limitations

In this chapter I compared established measures of body fat distribution (WC, WHR, and WHtR) and body composition (BF %, FMI, FFMI, and SMI) to BMI in their ability to predict mortality for 'healthier agers' within the seventh decade of life. This is one of the largest studies which has concurrently estimated the association for mortality for surrogate measures of adiposity, and body composition measures derived from bio-impedance. This work, therefore, adds further evidence to this limited research area on the mortality risks associated with measures of body fat distribution and body composition measures. The concordance between tertile measures was also presented, highlighting the variability of the proportions of different measures within the intermediate tertile of BMI, which corresponded to values within the BMI Overweight range.

There are several limitations with this analysis. One limitation of this analysis was that the outcome addressed was all-cause mortality. Risk estimates may differ for other health outcomes for the range of measures assessed in this chapter. This chapter focused on 'healthier agers' aged 60 to 69 years, therefore, the results may not be generally applicable to those younger or older than this age range. The participants included were predominately white British ethnicity and the results therefore may not be generalisable to wholly non-Caucasian populations. This analysis used sex-specific tertiles to enable comparisons between BMI, body fat distribution measures, and body composition measures rather than pre-defined thresholds.

Further work is needed to clarify the associations between measures of body fat distribution and body composition with other health outcomes. In this chapter I focused on comparing individual measures with mortality. Mortality risks may be improved by combining measures. In **Chapter 8** I use the UK Biobank to estimate associations between combined measures of BMI and waist-to-hip ratio (WHR) with mortality and incident coronary heart disease (CHD) for 'healthier agers' aged 60 to 69 years. This combination was chosen as BMI is one of the most widely used measures in clinical practice. Models with WHR tertiles achieved the lowest AIC values.

7.5.5. Conclusions

For ‘healthier agers’ within the seventh decade of life measures of fat distribution (WC, WHR, and WHtR) improved mortality prediction compared to models containing BMI. Persons with higher adiposity (measured overall or centrally) are at a substantially increased risk for mortality. The lowest concordance was found between tertiles of BMI and WHR tertiles

Supplementary material for Chapter 7

List of Tables for supplementary material Chapter 7

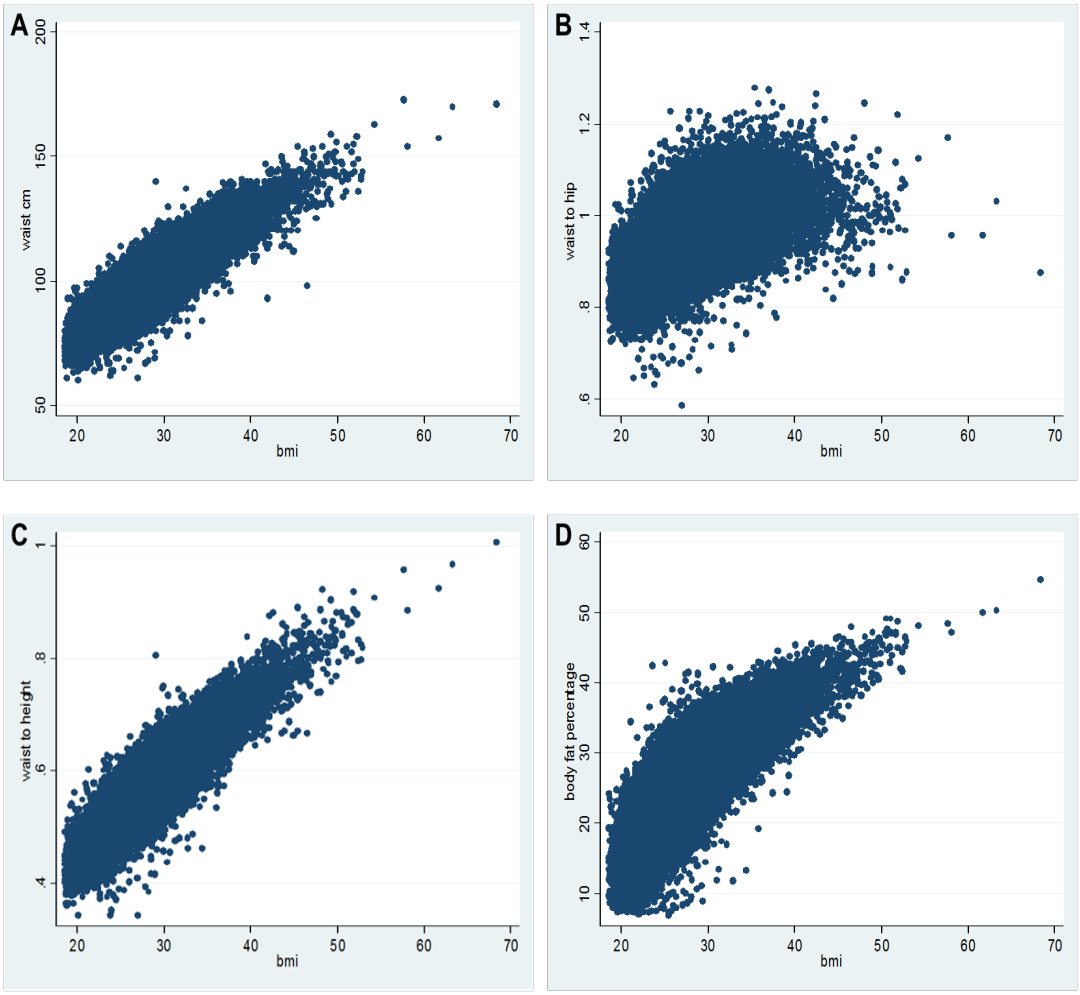
List of Figures for supplementary material Chapter 7

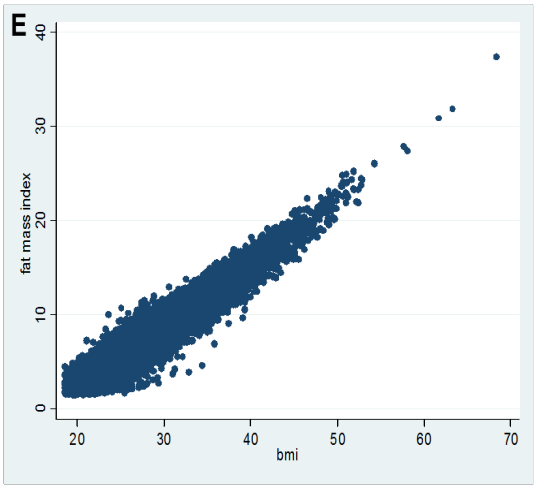
Table S7.1 Number of deaths per tertile of BMI, fat distribution measures, and body composition measures for 'healthier agers' aged 60 to 69 years from the UK Biobank

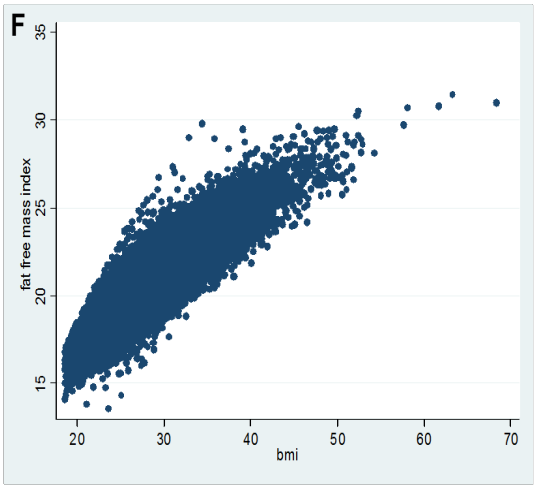
Measure	**Tertile 1**	**Tertile 2**	**Tertile 3**
BMI	889/45660	1008/45638	1273/45655
Waist circumference	938/49620	937/43389	1305/43924
Waist-to-hip ratio	841/45852	1018/45650	1321/45431
Waist-to-height ratio	853/45764	976/45568	1351/45601
Body fat percentage	887/45838	986/45835	1307/45260
Fat Mass Index	890/45660	980/45644	1310/45629
Fat Free Mass Index	992/45678	1003/45656	1185/45599
Skeletal Mass Index	1979/45647	964/45647	1127/45639

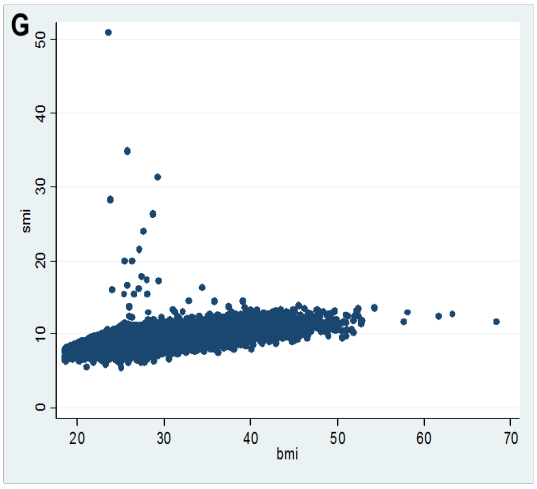
Note: 'Healthier agers' were non-smokers without recent cancer (except non-melanoma skin cancer), dementia, heart failure and survived the first 1.9 years. Persons with a BMI <18.5 kg/m^2 were excluded.

Figure S7.1 | Distribution of waist, waist-to-hip, waist-to-height, body fat percentage, fat mass index, fat free mass index, and skeletal mass index against BMI for male 'healthier agers' from the UK Biobank



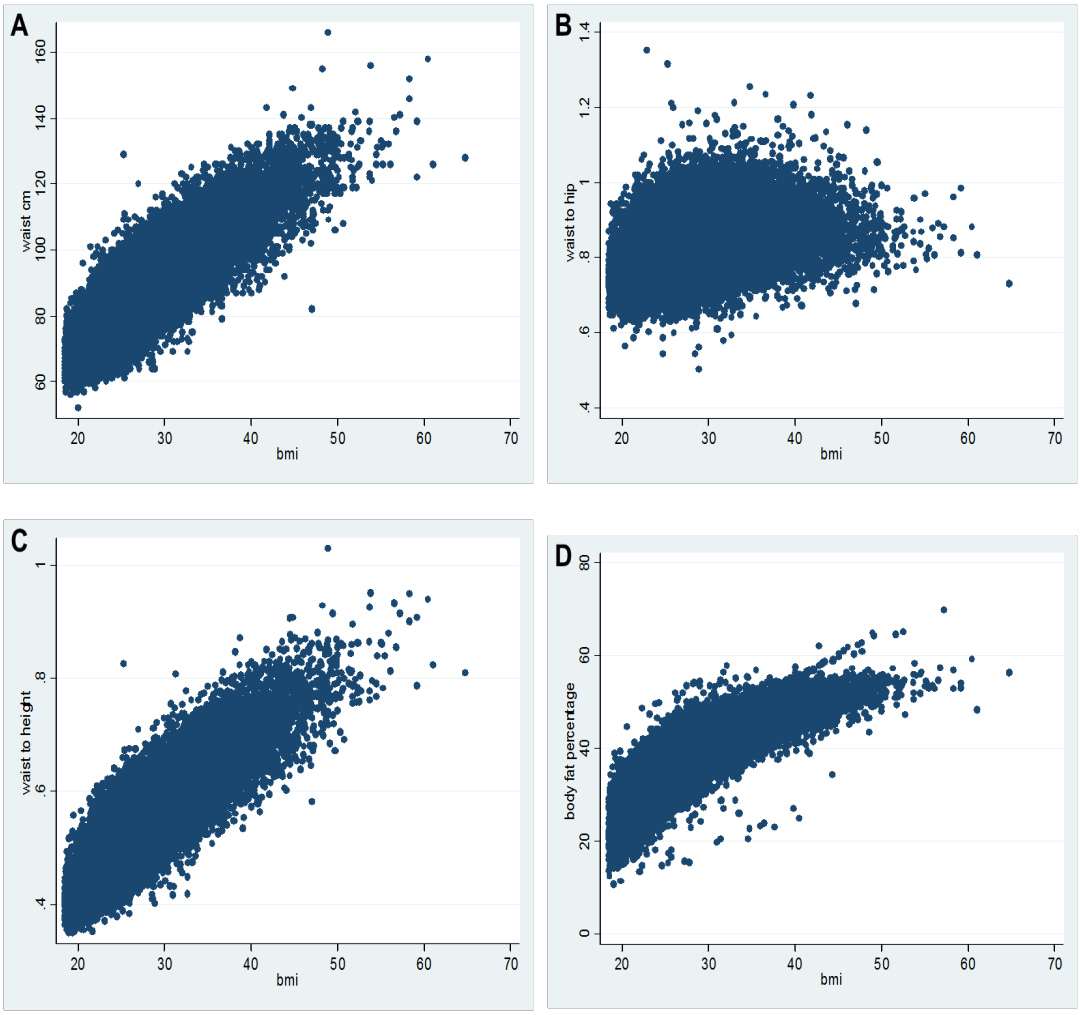


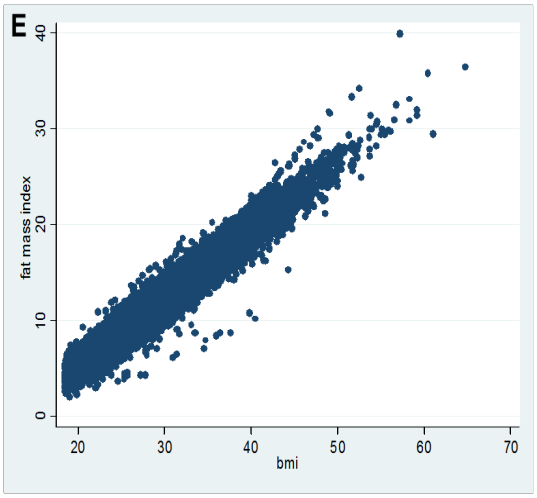


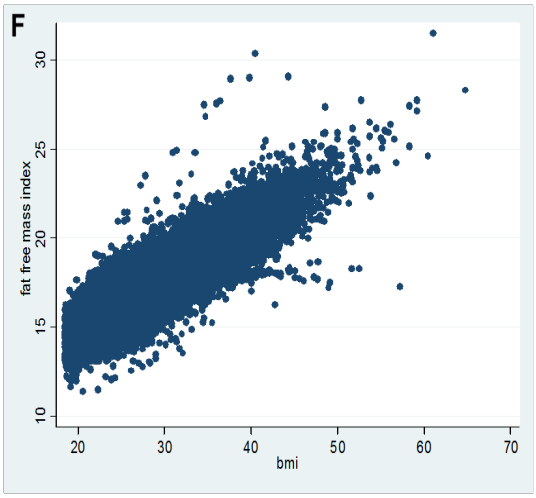


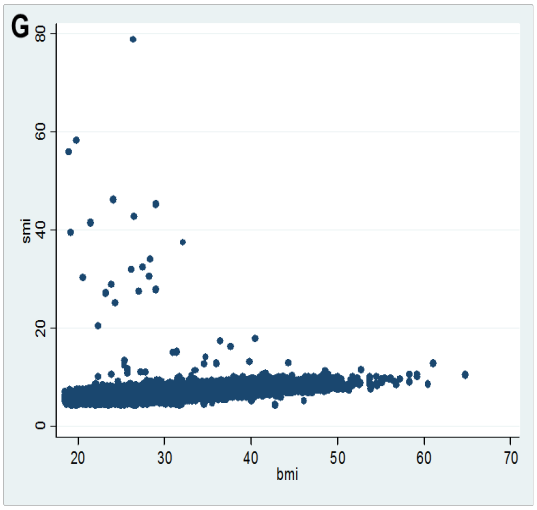
Note: 'Healthier agers' were non-smokers without recent cancer (except non-melanoma skin cancer), dementia, heart failure and survived the first 1.9 years. Models were adjusted for age, sex, alcohol intake, smoking history, and education WHR: waist-to-hip ratio; WHtR: waist-to-height ratio; BF%: body fat percentage; FMI: fat mass index; FFMI: fat free mass index; SMI: skeletal mass index. Persons with a BMI <18.5 kg/m^2 were excluded.

Figure S7.2 | Distribution of waist, waist-to-hip, waist-to-height, body fat percentage, fat mass index, fat free mass index, and skeletal mass index against BMI for female 'healthier agers' from the UK Biobank









Note: 'Healthier agers' were non-smokers without recent cancer (except non-melanoma skin cancer), dementia, heart failure and survived the first 1.9 years. Models were adjusted for age, sex, alcohol intake, smoking history, and education WHR: waist-to-hip ratio; WHtR: waist-to-height ratio; BF%: body fat percentage; FMI: fat mass index; FFMI: fat free mass index; SMI: skeletal mass index. Persons with a BMI <18.5 kg/m^2 were excluded.

Chapter 8 – Joint associations of BMI and central adiposity measures for mortality and coronary heart disease: follow-up of 130,473 UK Biobank participants

Table of Contents

List of Tables

List of Figures

8.1. Overview of the chapter

This chapter is based predominately on a published manuscript.

> **Bowman, K., Atkins, J.L., Delgado, J., Kos, K., Kuchel, G.A., Ble, A., Ferrucci, L., & Melzer, D. (2017) Central adiposity and the overweight risk paradox in aging: follow-up of 130,473 UK Biobank participants. AJCN. 06(1):130-135.**

My contribution to this manuscript included conducting the literature review, designing and conducting the analyses, and writing the manuscript. Therefore, much of this chapter is a direct translation from this paper. Some sentences have been modified to make them clearer. The terms used for describing the BMI categories and groups have also been altered to be consistent throughout this thesis. Additional sections have been added to the introduction and discussion to emphasise the links throughout this thesis.

8.2. Summary

Background: In later life (aged ≥65 years), persons within the body mass index (BMI) defined Overweight range (25.0-29.9 kg/m^2) have been reported to have reduced or similar mortality risks to those within the conventional BMI Normal range (18.5-24.9 kg/m^2). However, this paradox for mortality is partly explained by the inclusion of smokers and those with conditions associated with weight loss. The paradox may also arise from BMI failing to measure fat redistribution to a centralized position in later life. Combining BMI with abdominal adiposity measures may more accurately identify those at higher risks for adverse health outcomes.

Objective: To estimate associations between combined measures of BMI and waist-to-hip ratio (WHR) with mortality and incident coronary heart disease (CHD).

Design: This analysis included 130,473 'healthier agers' aged 60 to 69 years enrolled in the UK Biobank (baseline 2006-2010) with a BMI in the range 18.5-34.9 kg/m^2. 'Healthier agers' were non-smokers without conditions associated with weight loss or reported weight loss and who survived the first two years of follow-up. Population and sex specific WHR tertiles were derived from baseline measures. For men, these were 'lower' <0.91 and 'higher' ≥0.96, and for women these were 'lower' <0.79 and 'higher' ≥0.85. Cox proportional hazards and competing risks models were adjusted for age, sex, alcohol intake, smoking history and education.

Results: Ignoring WHR, those within the BMI Overweight range had similar mortality risks relative to those within the BMI Normal range (Hazard ratio [HR] 1.09 95% Confidence Interval [CI] 0.99, 1.19, p=0.066). However, those within the BMI Normal range plus higher WHR tertile had an increased mortality risk (HR 1.33 CI 1.08, 1.65) relative to the referent group, consisting of those within the BMI Normal range plus lower WHR tertile. Those within the BMI Overweight range plus higher WHR tertile had increased mortality risks (HR 1.41 CI 1.25, 1.61) relative to the referent group, with increased risks for incident CHD (Sub

HR [SHR] 1.64 CI 1.39, 1.93). There was no interaction for mortality between physical activity and the combined BMI and WHR groups.

Conclusions: For healthier agers (i.e. non-smokers, without conditions associated with weight loss) being within the BMI Normal or BMI Overweight range but also having central adiposity is associated with substantial excess mortality. The claimed BMI Overweight risk paradox may in part result from failing to account for central adiposity, rather than reflecting a protective physiological effect of higher body fat content in later life.

8.3. Introduction

The prevalence of body mass index (BMI) defined Overweight (25.0-29.9 kg/m^2) and Obesity (≥30.0 kg/m^2) in adults has increased dramatically since 1980, with an estimated 2.1 billion adults affected globally in 2013 (Ng *et al.*, 2014). Younger and middle aged adults within the BMI Overweight or BMI Obese-1 (30.0-34.9 kg/m^2) ranges have substantially increased mortality risks, relative to those within the conventional BMI Normal range (18.5-24.9 kg/m^2) (Whitlock *et al.*, 2009; Berrington de Gonzalez *et al.*, 2010). However, paradoxical associations for those within the BMI Overweight and BMI Obese-1 ranges have been reported in adults ≥65 years; several meta-analyses and cohort studies showed that the BMI Overweight range was associated with reduced (Flegal *et al.*, 2013; Winter *et al.*, 2014) or similar mortality risks (Janssen and Mark, 2007; Pischon *et al.*, 2008; Bea *et al.*, 2015) to those within the BMI Normal range. Some researchers have claimed that this paradox may reflect a protective physiological effect of slightly higher BMI (Dixon *et al.*, 2015) and challenged the idea that conventional BMI thresholds should be used in older persons (Janssen and Mark, 2007; Flicker *et al.*, 2010; Dixon *et al.*, 2015; Peter *et al.*, 2015) arguing that this paradox justifies a major revision of the current scientific consensus on the health dangers of being Overweight. Others have claimed that public health researchers 'would rather not talk about' studies that show that being Overweight does not always shorten life (Hughes, 2013).

In **Chapters 4** and **5** I presented analyses of 955,000 population representative primary care patients and showed that paradoxical BMI Overweight and BMI Obese-1 mortality risks for adults aged 60 to 84 years were partly explained by the inclusion of smokers and patients with conditions associated with weight loss. The inclusion of this population can result in confounding, in which certain disease processes that carry higher risk of death also cause weight loss. This weight loss can occur even before diagnoses are made and can thereby distort risk estimates. In 'healthier agers' (non-smokers without conditions associated with weight loss), BMI Obese-1 was associated with excess mortality and coronary heart disease (CHD), i.e. the BMI Obesity risk paradox reversed.

A further possible bias in the paradoxical associations for those within the BMI Overweight (and BMI Obese-1) range(s) may be that BMI does not distinguish between fat and fat free mass (Snijder *et al.*, 2006; Janssen and Mark, 2007) or the distribution of fat mass. This limitation of BMI may be accentuated in older age groups; after 60 years, fat-free mass decreases and fat mass is redistributed (Kuk *et al.*, 2009; St-Onge and Gallagher, 2010) to a more central position. Therefore, in older adults, those within the BMI Normal range might include people with higher fat mass and lower fat free mass. Elevations in waist circumference (WC), waist-to-hip ratio (WHR), and waist-to-height ratio (WHtR) have been reported to be associated with incident CHD (Taylor *et al.*, 2010; Kizer *et al.*, 2011; Wormser *et al.*, 2011). However, findings of increased mortality risks with elevated WC or WHR have been inconsistent among older adults, with no associations (Baik *et al.*, 2000; Dolan *et al.*, 2007; Batsis, Singh and Lopez-Jimenez, 2014) or inverse associations found in men only (Reis *et al.*, 2009).

In **Chapter 7** I presented an analysis using the UK Biobank to compare established measures of body fat distribution (WC, WHR, and WHtR) and body composition (body fat percentage [BF%], fat mass index [FMI], fat free mass index [FFMI], and skeletal mass index [SMI]) to BMI for mortality prediction for 'healthier agers' within the seventh decade of life. 'Healthier agers' were non-smokers without conditions (cancer, dementia or heart failure) associated with weight loss or reported weight loss and who survived the first two years of follow-up. The analysis showed that measures of body fat distribution improved mortality prediction compared to models containing BMI. The lowest AIC value (preferred model) was achieved for the model containing WHR tertiles. Overall my analysis provided further evidence that 'healthier agers' with higher adiposity (measured overall or centrally) are at a substantially increased risk for mortality.

In **Chapter 7** I also highlighted the variability in the proportions of the alternative measures of body fat distribution and body composition for those within the intermediate tertile of BMI which corresponded to BMI values within the Overweight range. The lowest concordance (i.e. a person being in both the BMI lower tertile and WHtR lower tertile) was found between BMI tertiles and WHR

tertiles for those within the intermediate or higher tertiles for both measures. The lowest concordance for the lower BMI tertile was found with SMI tertiles.

Several previous analyses have estimated the risks for mortality or coronary heart disease by either mutually adjusting for general adiposity (e.g. BMI) and measures of fat distribution (WC and WHR) or cross classified participants. Increased mortality risks have been reported for higher waist circumference values (Janssen, Katzmarzyk and Ross, 2005; Pischon *et al.*, 2008) and WHR values (Pischon *et al.*, 2008) after adjustment for BMI. Increased risks for incident coronary heart disease with higher waist circumference values or WHR values have been reported for females aged ≥65 years after adjustment for BMI (Canoy *et al.*, 2007). However, no significant associations for coronary heart disease have been reported for males aged ≥65 years for body fat distribution measures after adjustment for BMI (Rexrode, Buring and Manson, 2001; Canoy *et al.*, 2007). Studies assessing the combined associations of BMI plus body fat distribution measures with mortality have not been consistent. One study showed no associations between combined BMI and WHR categories for adults aged 65 to 102 years (Reis *et al.*, 2009). In contrast a meta-analysis by de Hollander *et al.*, (2012) showed that after combining BMI and waist circumference categories, there were increased mortality risks for those within the higher waist circumference categories across the BMI groups for adults aged ≥65 years (de Hollander *et al.*, 2012 a).

Overall there has been a paucity of recent studies which have used combined BMI and central adiposity measures for assessing mortality and coronary heart disease risks. The limited studies in this area have been inconsistent. Here I aimed to estimate the associations between combined BMI and central adiposity measures with mortality and incident CHD in a large older cohort. The central adiposity measure chosen for the main analyses was WHR as it is a well-recognised measure of central adiposity (Snijder *et al.*, 2006) and has a relatively weak correlation with BMI (compared to waist circumference alone) (Pischon *et al.*, 2008; Taylor *et al.*, 2010). Furthermore, in **Chapter 7** I showed the preferred model for mortality for 'healthier agers' was one which contained tertile measures of WHR. The UK Biobank offers an ideal opportunity to estimate these

associations in a large sample of 'healthier agers' (non-smokers, without conditions associated with weight loss) in their seventh decade, in whom distribution of fat stores to a more central distribution is measured.

8.4. Methods

8.4.1. Participants

Between 2006 and 2010 the UK Biobank recruited over 500,000 volunteers across England, Wales and Scotland; the great majority of respondents were aged 40 to 69 years (range 37 to 73 years). At baseline the participants provided self-reports for demographic, socioeconomic, and lifestyle factors. Participants also had a range of physical measures taken at the baseline visit including anthropometrics and blood samples (UK Biobank, 2007; Sudlow *et al.*, 2015). The overall response rate was 5.5% and participants provided informed consent to have their records linked to cancer registrations, hospital admissions, and death registries.

For this analysis participants aged 60 to 69 years at recruitment were included as highlighted in the previous chapter (**7**) the UK Biobank aimed to recruit participants aged 40 to 69 years, with 2,247 participants aged >69 years by the time of their assessment visit (UK Biobank, 2007). Only those aged 60 to 69 were selected as the obesity paradox has been reported predominantly for this and older groups. Most women participants were postmenopausal. Additionally, fat mass re-distribution to a more central deposition is generally well established in this age-group.

Participants who were missing BMI (n = 1,299), waist circumference (n = 44) or hip circumference measures (n =20) were excluded. Participants with a BMI value <18.5 kg/m^2 or BMI ≥ 35 kg/m^2 (n = 14,926) were excluded as the paradox has predominately been reported for those with BMI values within the Overweight (25.0-29.9 kg/m^2) and Obese-1 (30.0-34.9 kg/m^2) ranges.

Participants with missing responses to questions on alcohol intake, educational attainment, or smoking status were excluded (n = 5,019). To account for subjects

with conditions associated with weight loss or altered body distribution, current smokers, and patients who had a previous diagnosis of cancer, heart failure, or dementia (*n* = 38,991) were excluded. The associations of 15 major diagnoses with measured weight loss in a large sample (*n* = 955,000) of primary care patients were empirically tested in **Chapter 4**: cancer, heart failure, and dementia conferred the highest odds ratios (≥1.5) for measured weight loss. The resulting group consists of 'healthier agers' for whom population level obesity prevention may be relevant. Diagnoses at or before baseline were derived from participants' self reports, cancer registries, and hospital admissions (in-patients). Participants who died but had no associated death date (*n* = 1) were excluded. The first two years of follow-up (*n* = 677) were excluded to reduce the effects of reverse causation whereby underlying diseases are associated with a lower BMI and an increased risk of death. Participants who reported at baseline having lost weight compared to 1 year previously, didn't know, or preferred not to answer (*n* = 23,662) were excluded; previous weight loss has been shown to be associated with adverse outcomes. The question on weight loss at baseline did not ask about the degree of weight change or whether this weight change was intentional or unintentional. This exclusion therefore covered more substantial weight losses as well as minor losses. The remaining sample for analysis therefore included 130,473 participants (62,418 men and 68,055 women).

8.4.2. Exposures

Height, weight, waist and hip circumferences were measured at the baseline examination. The natural indent (umbilicus was used if the natural indent could not be observed) was measured for the waist circumference. The hip circumference was recorded at the widest part of the hips (UK Biobank, 2014). Body mass index and waist-to-hip ratio were derived from the baseline measures. The World Health Organization (WHO) BMI Classification was used, i.e. Normal weight (18.5-24.9 kg/m^2), Overweight (25.0-29.9 kg/m^2) and Obese-1 (30.0-34.9 kg/m^2) (World Health Organization, 2000). WHR was categorised by population and sex-specific tertiles; 'lower' (men <0.91, women <0.79), 'intermediate' (men 0.91 to <0.96, women 0.79 to <0.85) and 'higher' (men ≥0.96, women ≥0.85). The proposed WHO binary WHR cut points for abdominal Obesity of >0.85 for females and >0.90 for males were also used (World Health Organization, 2008).

8.4.3. Lifestyle factors, educational attainment, and ethnicity

Lifestyle factors included alcohol intake, smoking history (never or previous), and physical activity. Education was based on the highest educational attainment. These factors had previously been defined and details on the categories are documented in **Chapters 2** and **7**. Ethnicity was categorized as White, Mixed, Asian, Black, Chinese, and other. The Mixed category combined the responses of the UK Biobank ethnicity questions of 'mixed', 'White and Black Caribbean', 'White and Black African', 'White and Asian' and 'Any other mixed background'.

8.4.4. Outcomes

Death certificate data was available up to August 15th 2015. For the English and Welsh participants this was collected by the Health and Social Care Information Centre (HSCIC) and for Scottish participants this was collected by the Information Services Department (ISD). Incident coronary heart disease (ICD-10 codes I20-I25) was available up to February 27th 2015 from Hospital Episode Statistics (HES, England), Scottish Morbidity Record (SMR, Scotland), and the Patient Episode Database for Wales (PEDW, Wales).

8.4.5. Statistical analysis

Pearson Correlation analysis was used to evaluate the correlations between the anthropometric measures. For categorical mortality analyses (BMI categories, WHR tertiles, and the joint associations of BMI and WHR) Cox proportional hazards models were used. The follow-up time for the mortality risks was computed from the assessment date until the date of death, or until August 15th 2015 (for survivors). Schoenfeld residuals were used to test the proportional hazards assumption. Competing risks models (accounting for mortality) were used to estimate the association between the anthropometric measures and incident coronary heart disease. The follow up time for incident CHD risks was computed from the assessment date until the date of incident CHD, date of death, or until February 27th 2015. Multivariate models were adjusted for age, gender, alcohol intake, never or previous smoker, and educational attainment. These variables were chosen as they are in line with previous reports and similar to those chosen for the analyses in **Chapter 4** and **Chapter 5**. The Akaike Information Criteria (AIC) was obtained for each model, with lower AIC values

generally indicating improved model fits. Physical activity, age (60 to 64 years and 65 to 69 years), smoking history and gender interactions with the combined associations of BMI plus WHR tertiles were assessed. Analyses were carried out using Stata statistical software (version 13.1) and R version 3.2.0 with the packages ("metafor" version 1.9-9).

8.5. Results

8.5.1. Baseline characteristics

Table 8.1 presents the baseline characteristics of the study population (*n* = 130,473). The mean BMI was 26.9 kg/m^2 (SD 3.4 kg/m^2), 48.9 % were classified as being within the BMI Overweight range, and 19.5% as being within the BMI Obese-1 range. The mean WHR was 0.82 (SD 0.07) for women and 0.94 (SD 0.06) for men. The correlation between BMI and WHR was r=0.58 in men, and r= 0.44 in women. Sex specific tertiles of WHR were defined and derived from the overall study population as follows: 'lower' (men <0.91, women <0.79), intermediate (men 0.91 to <0.96, women 0.79 to <0.85) and 'higher' (men ≥0.96, women ≥0.85) WHR. For participants in the BMI Normal range 57.7% had a lower WHR and 12.8% had a higher WHR, in the BMI Overweight range, 27.1% had a lower WHR and 35.2% had a higher WHR, and within the BMI Obese-1 range 9.6% had a lower WHR and 62.0% had a higher WHR (supplementary material Table S8.1).

Table 8.1 | Baseline characteristics of the 'healthier agers' aged 60 to 69 years (*n* = 130,473) from the UK Biobank

Variables	***n* = 130,473**
Age years, mean (SD)	64.1 (2.8)
Gender	
Females, *n* (%)	68,055 (52.2)
BMI, mean (SD)	26.9 (3.4)
BMI (kg/m^2), n (%)	
18.5-24.9	41,369 (31.7)
25.0-29.9	63,731 (48.9)
30.0-34.9	25,373 (19.5)
WHR, mean (SD)	
Females, mean (SD)	0.82 (0.07)
Males, mean (SD)	0.94 (0.06)
Alcohol intake frequency, n (%)	
Never	9,845 (7.6)
Special occasions only	13,973 (10.7)
One to three times a month	12,393 (9.5)
Once or twice a week	31,348 (24.0)
Three or four times a week	30,818 (23.6)
Daily or almost daily	32,096 (24.6)
Smoking status, n (%)	
Never	72,419 (55.5)
Previous	58,054 (44.5)
Education, n (%)	
None	33,157 (25.4)
CSEs	2,353 (1.8)
GCSEs/O-levels	18,627 (14.3)
A-levels/NVQ/HND/HNC	19,318 (14.8)
Professional Qualification	20,862 (16.0)
College or University degree	36,156 (27.7)

Table 8.1 continued

Variables	***n* = 130,473**
Diagnosed disease at baseline, n (%)	
Coronary Heart Disease	10,115 (7.8)
Type 2 Diabetes	6,781 (5.2)
Follow-up years, mean (SD)	6.5 (0.9)

Note: 'Healthier agers' were non-smokers without recent cancer (except non-melanoma skin cancer), dementia, heart failure and survived the first 1.9 years

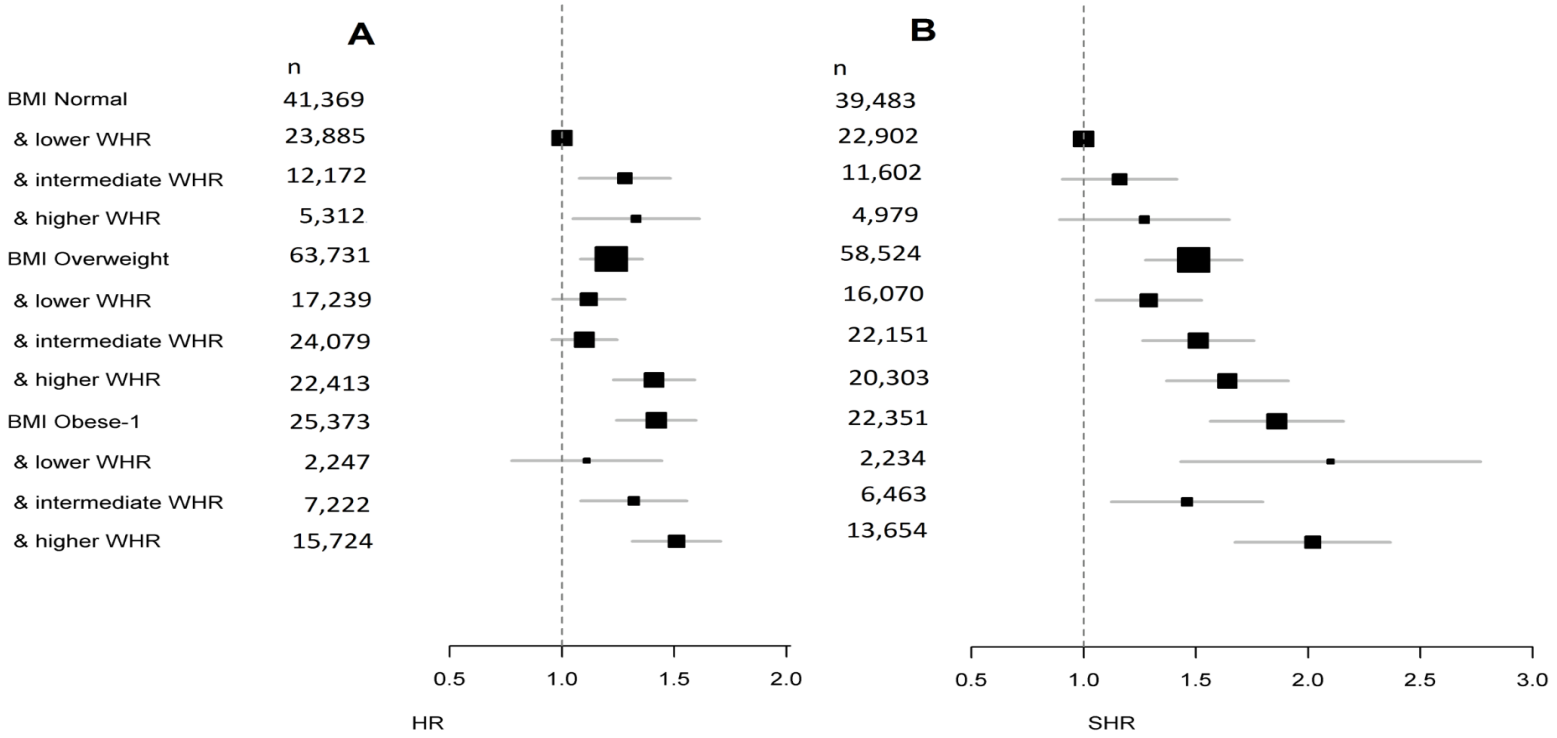
8.5.2. Mortality

Over a maximum follow-up period of 8.3 years 2,974 adults died (mean follow-up period 6.5 years SD 0.9 years). In survival models adjusted for age, sex, never or former smoker, alcohol intake, and level of education, those within the BMI Overweight range were not at a significantly increased risk for mortality (HR 1.09 95% CI 0.99, 1.19 p=0.066) relative to those within the conventional BMI Normal range. Those within the BMI Obese-1 range had a substantially increased mortality risk HR 1.27 (CI 1.14, 1.41) relative to those within the conventional BMI Normal range. Compared to those within the lowest tertile of WHR, those within the intermediate tertile had a 12% increased risk for mortality (CI 1.01, 1.23), and those within the highest tertile had a 36% increased risk for mortality (CI 1.24, 1.49). These associations with WHR tertiles were attenuated after adjustment for BMI category (intermediate WHR tertile HR 1.10 CI 1.00, 1.21, higher WHR tertile HR 1.32 CI 1.19, 1.46).

8.5.3. Combined associations of BMI categories and WHR tertiles with mortality

The mortality model fit was improved when both BMI and WHR were included compared to a model with BMI only. **Figure 1A** shows the joint association of BMI category and WHR tertiles for mortality (supplementary material Table S8.2). Those within the BMI Normal range plus higher WHR tertile had an increased mortality risk (HR 1.33 CI 1.08, 1.65) compared to the referent group consisting of those within the BMI Normal range plus lower WHR tertile. Also, compared to adults within the BMI Normal range plus lower WHR, there was an increased mortality risk of 22% for the overall (not accounting for WHR) BMI Overweight range (CI 1.09, 1.36), and 42% for the overall BMI Obese-1 range (CI 1.25, 1.61). Those within the BMI Overweight range plus higher WHR tertile had a 41% increased mortality risk (CI 1.25, 1.61) and those within the BMI Obese-1 range plus higher WHR tertile had a 51% increased mortality risk (CI 1.32, 1.73) relative to those within the BMI Normal range plus lower WHR tertile.

Figure 8.1 | Hazard and sub-Hazard ratios for mortality **(A)** and coronary heart disease **(B)** for combined BMI categories and waist-to-hip tertiles for 'healthier agers' aged 60 to 69 years from the UK Biobank (*n* = 130,473)



Note: 'Healthier agers' were non-smokers without recent cancer (except non-melanoma skin cancer), dementia, heart failure and survived the first 1.9 years. Competing risk models were used to estimate the association for incident coronary heart disease which account for mortality during the follow-up. Cox proportional hazards and competing risk models were adjusted for age, sex, alcohol intake, smoking history and education. The reference group was those within the BMI Normal range with lower WHR. Sex specific tertiles of WHR were defined and derived from the overall study population as follows: lower (men <0.91, women < 0.79), intermediate (men 0.91 to <0.96, women 0.79 to <0.85) and higher (men ≥0.96, women ≥ 0.85). WHR: waist-to-hip, SHR: sub-Hazard Ratio

8.5.4. Interactions

There was no significant interaction between the joint associations of BMI and WHR tertiles with age group (60 to 64 years and 65 to 69 years), gender, physical activity, or smoking history (never or former) for mortality.

8.5.5. Coronary heart disease

At baseline, there were 10,115 prevalent cases of coronary heart disease (CHD) and these were excluded from the competing risks analysis for incident CHD with 120,358 participants analysed (incident CHD cases *n* = 1,878). **Figure 1B** shows the joint association of the BMI categories and WHR tertiles for CHD (supplementary material Table S8.2)**.** There was an increased risk for incident CHD for those within the BMI Overweight range plus higher WHR (SHR 1.64 CI 1.39, 1.93) relative to those within the BMI Normal plus lower WHR. Additionally, there was an increased risk for those within the lower WHR and intermediate WHR for those within the BMI Overweight range. Within the BMI Obese-1 range, there were increased risks for incident CHD for all the WHR tertiles.

8.5.6. Sensitivity analyses

The main analysis was also run (for the joint association of BMI and WHR tertiles) with age as the underlying time scale, but the results were not substantially changed (**Table 8.2**).

Table 8.2 | Joint association of the BMI categories and WHR tertiles with mortality using age as the time scale for 'healthier agers' aged 60 to 69 years (*n* = 130,473) from the UK Biobank

BMI range and WHR tertile [1]	**Mortality HR (95% CI)**
Normal and lower WHR	Ref
Normal and intermediate WHR	1.26 (1.07, 1.47)
Normal and higher WHR	1.30 (1.05, 1.60)
Overweight and lower WHR	1.13 (0.98, 1.30)
Overweight and intermediate WHR	1.09 (0.96, 1.24)
Overweight and higher WHR	1.38 (1.22, 1.57)
Obese-1 and lower WHR	1.13 (0.84,1.53)
Obese-1 and intermediate WHR	1.32 (1.11, 1.58)
Obese-1 and higher WHR	1.50 (1.31, 1.72)

[1] *WHR was categorised by population and sex-specific tertiles, lower (men <0.91, women < 0.79), intermediate (men 0.91 to <0.96, women 0.79 to <0.85) and higher (men ≥0.96, women ≥0.85)*

Note: 'Healthier agers' were non-smokers without recent cancer (except non-melanoma skin cancer), dementia, heart failure and survived the first 1.9 years Cox proportional hazard models were adjusted for gender, smoking history, alcohol intake, and educational attainment. Age was used as the time scale. WHR: waist-to-hip ratio.

The proposed WHO WHR cut points for abdominal Obesity (World Health Organization, 2008) >0.85 for women and >0.90 for men (**Table 8.3**) was also analysed. There was a 22% increased mortality risk (HR 1.22 CI 1.09, 1.37) for those within the BMI Overweight range plus higher WHR group and a 42% increased mortality risk (HR 1.42 CI 1.26, 1.61) for those within the BMI Obese-1 range plus higher WHR group relative to those within the BMI Normal range plus lower WHR. An analysis using a higher threshold for the males of WHR >1.00 was also ran, as with the WHO cut points over 75% of the males were classified as centrally Obese. The point estimates were higher for those within the BMI Overweight range plus higher WHR and for those within the BMI Obese-1 range plus higher WHR (**Table 8.3**).

Table 8.3 | Joint association of the BMI categories with binary WHR cut points and higher threshold WHR cut points with mortality for 'healthier agers' aged 60 to 69 years (*n* = 130,473) from the UK Biobank

BMI range and WHR category	**WHO cut points[1] HR (95% CI)**	**Higher threshold cut points[2] HR (95% CI)**
Normal and low WHR	Ref	Ref
Normal and high WHR	1.25 (1.07, 1.45)	1.20 (0.94, 1.53)
Overweight and low WHR	1.10 (0.96, 1.25)	1.02 (0.92, 1.12)
Overweight and high WHR	1.22 (1.09, 1.37)	1.40 (1.23, 1.59)
Obese-1 and low WHR	1.16 (0.94, 1.44)	1.14 (1.00, 1.29)
Obese-1 and high WHR	1.42 (1.26, 1.61)	1.48 (1.30, 1.68)

[1] Cut points for waist-to-hip ratio category for women were low WHR ≤0.85 and for men were low WHR ≤0.90.
[2] Cut points for waist-to-hip ratio category for women were low WHR ≤0.85 and for men were low WHR ≤1.00.

Note: 'Healthier agers' were non-smokers without recent cancer (except non-melanoma skin cancer), dementia, heart failure and survived the first 1.9 years Cox proportional hazard models were adjusted for age, gender, smoking history, alcohol intake, and educational attainment. WHR: waist-to-hip ratio

Restricting the analyses to participants who responded that their ethnic background was White/British (*n* = 120,151) only marginally changed the results for BMI and WHR for mortality (**Table 8.4**): unfortunately models for other ethnic groups were underpowered.

Table 8.4 | Joint associations of the BMI categories and WHR tertiles with mortality for 'healthier agers' identifying as 'white' British aged 60 to 69 years (*n* = 120,151) from the UK Biobank

BMI range and WHR tertile [1]	**White British HR (95% CI)**
Normal and lower WHR	ref
Normal and intermediate WHR	1.25 (1.06, 1.47)
Normal and higher WHR	1.28 (1.02, 1.60)
Overweight and lower WHR	1.10 (0.95, 1.27)
Overweight and intermediate WHR	1.08 (0.94, 1.24)
Overweight and higher WHR	1.38 (1.21, 1.57)
Obese-1 and lower WHR	1.10 (0.80, 1.50)
Obese-1 and intermediate WHR	1.28 (1.07, 1.54)
Obese-1 and higher WHR	1.52 (1.33, 1.75)

[1] WHR was categorised by sex-specific tertiles, lower (men <0.91, women < 0.79), intermediate (men 0.91 to <0.96, women 0.79 to <0.85) and higher (men ≥0.96, women ≥0.85)

Note: 'Healthier agers' were non-smokers without recent cancer (except non-melanoma skin cancer), dementia, heart failure and survived the first 1.9 years Cox proportional hazard models were adjusted for age, gender, smoking history, alcohol intake, and educational attainment. WHR: waist-to-hip ratio

Restricting the analyses to weight stable participants (*n* = 93,764) did not substantially change the results (**Table 8.5).**

Table 8.5 | Joint associations of the BMI categories and WHR tertiles with mortality for 'healthier agers' aged 60 to 69 years who responded that their weight was the same as one year previously i.e. weight stable (*n* = 93,764) using the UK Biobank

BMI range and WHR tertile [1]	**Weight stable HR (95% CI)**
Normal and lower WHR	ref
Normal and intermediate WHR	1.24 (1.04, 1.47)
Normal and higher WHR	1.39 (1.10, 1.75)
Overweight and lower WHR	1.17 (1.00, 1.37)
Overweight and intermediate WHR	1.15 (0.99, 1.33)
Overweight and higher WHR	1.42 (1.23, 1.64)
Obese-1 and lower WHR	0.91 (0.58, 1.43)
Obese-1 and intermediate WHR	1.33 (1.06, 1.66)
Obese-1 and higher WHR	1.64 (1.39, 1.92)

[1] WHR was categorised by sex-specific tertiles, lower (men <0.91, women <0.79), intermediate (men 0.91 to <0.96, women 0.79 to <0.85) and higher (men ≥0.96, women ≥0.85)

Note: 'Healthier agers' were non-smokers without recent cancer (except non-melanoma skin cancer), dementia, heart failure and survived the first 1.9 years Cox proportional hazard models were adjusted for age, gender, smoking history, alcohol intake, and educational attainment. WHR: waist-to-hip ratio

8.6. Discussion

There is much discussion in the literature about whether or not being Overweight, as defined by BMI, is a risk factor for coronary heart disease and all-cause mortality in later life. Here I estimated the associations between combined BMI and central adiposity measures with mortality and incident coronary heart disease, in a large older cohort of healthier agers. Firstly, models including both BMI and WHR were substantially more informative compared to models accounting for BMI only. For example, those within the BMI Normal range plus higher WHR tertile had an increased mortality risk (HR 1.33 CI 1.08, 1.65) compared to those within the BMI Normal range plus lower WHR tertile. The analyses showed that those within the BMI Overweight range plus higher WHR tertile experienced markedly raised risks for all-cause mortality relative to those within the BMI Normal range plus lower WHR tertile. There was also an increased risk of incident coronary heart disease with increasing WHR tertile for those within the BMI Overweight range. For those within the BMI Obese-1 range, mortality risks were raised and not paradoxical overall, and increasing tertiles of WHR also increased the risk for mortality within the BMI Obese-1 range.

It is clear from this analysis that higher central adiposity for those within the BMI Normal range and the BMI Overweight range should be considered as risk factors for clinical risk assessment and public health purposes in healthy agers. The findings suggest that the reported risk paradox of being overweight in older persons (overweight associated with lower mortality) may be due to failure to account for central adiposity, a feature that is not captured by BMI. Controlling or reducing adiposity to increase the chances of aging well (or successful aging) is of relevance to the studied group of healthier agers. The findings presented in this chapter therefore do not support the theory that the BMI Overweight risk paradox in healthy agers is a real protective physiological effect (Dixon *et al.*, 2015).

8.6.1. Comparison to previous literature

The results are difficult to compare with previous work, due to different inclusion/exclusion criteria, cut points use for waist-to-hip ratio, inclusion of varying older age-ranges, and varying follow-up periods. The results on the

association between WHR tertiles and mortality contrast with the non-significant associations for the middle and high tertiles reported for mortality for adults aged ≥60 years (*n* = 1,569) from NHANES III (Batsis, Singh and Lopez-Jimenez, 2014). This could be due to their relatively small sample size and their wider age-range, which may have weakened the associations. The results on the joint association between WHR and BMI categories differ to those by Reis *et al.*, (2009) who reported no increased risks for mortality for adults with enlarged WHR tertiles across the BMI Normal, Overweight, and Obese ranges for adults aged 65 to 100 years, again in a relatively small sample size (*n* = 3,748) from NHANES III (Reis *et al.*, 2009). The findings for the combined associations between WHR and BMI categories for coronary heart disease are also difficult to compare with previous studies as the analysis presented in this chapter used the recommended competing risk model analysis approach, accounting for mortality.

8.6.2. Strengths and limitations

Strengths of the analyses include the large sample of 'healthier agers', and the availability of anthropometric measures at baseline. Also, outcomes ascertainment was through the national death certificate system and hospital records, and is likely to be robust with no loss to follow-up, thus avoiding a common bias in aging cohorts (Chatfield, Brayne and Matthews, 2005).

The study inevitably has limitations including the use of a volunteer sample, albeit with a wide range of relevant risk exposures (Sudlow *et al.*, 2015). The UK Biobank did not aim for population representativeness but due to the wide variation in exposures included in the large sample at baseline, it is likely that the longitudinal risk estimates are relevant for the wider population (Allen *et al.*, 2012; Manolio *et al.*, 2012). The sample was predominately white British (92%), which may limit the generalizability to different Caucasian populations. The analysis was restricted to a 'healthier agers' group and the risk estimates may be inflated relative to the overall population, due to there being fewer competing risk factors (Stokes and Preston, 2016a), although the exclusions were designed to remove confounding and reverse causation. Also, this group of 'healthier agers' is the main potential target for primary prevention of obesity in later life.

Data on recent weight loss or weight change in the previous twelve months were based on participant's self-reports at baseline. It would have been preferable to exclude persons with weight loss over a longer time frame and to have had an indication on the severity of weight change, but data on these were unavailable. Alley *et al*., (2010) reported that during the last nine years of life there was an acceleration of the rate of weight loss for males aged ≥60 years from the Baltimore Longitudinal Study of Aging (Alley *et al.*, 2010), so the exclusion of any weight loss in the previous year should have accounted for this effect. Stokes and Preston (2016) have reported that estimates using baseline BMI may underestimate the association between obesity and mortality as BMI fluctuations throughout life are not captured; model performance was improved using a person's maximum attained BMI (Stokes and Preston, 2016b). Unfortunately, the UK Biobank did not collect data on weight history throughout the life course, so the results from the available BMI data may be underestimates of true effect sizes. The follow-up period of up to 8.3 years is comparable to other studies but longer follow-ups may be more informative. Relatively few of those within the BMI Obese-1 range had lower WHR, although many of those within the BMI Normal range did have intermediate or higher WHRs.

8.6.3. Future work

Future work might include a more extensive analysis in a wider age-range and with longer follow-up times. With the accumulation of longer follow-up times in UK Biobank, well-powered cause-specific mortality estimates should become feasible. Overall, much work is needed to develop and test effective interventions to limit or reduce excessive adiposity in older groups for whom major gains in healthy aging may thereby be attainable.

8.7. Conclusions

In this large sample of 60 to 69 year olds free of smoking and prior weight loss (or related disease), risk estimation models for mortality combining BMI and WHR were substantially more informative than models with only BMI measures. The reported BMI based overweight risk paradox in later life appears to be due in part to central adiposity, which is not measured by BMI. 'Healthier agers' (i.e. non-smokers without weight loss) with higher central adiposity within the BMI Overweight range have substantial excess mortality and coronary heart disease risks. There was no evidence of a risk paradox within the BMI Obese-1 range, but instead overall increases in mortality relative to those within the BMI Normal range with lower WHR. Overall the findings do not support acceptance of the BMI Obese or Overweight risk paradox as a real protective physiological effect in the studied older group.

Supplementary material Chapter 8

List of tables for supplementary material Chapter 8

Table S8.1 | Characteristics of the 'healthier agers' aged 60 to 69 years (*n* = 130,473) from the UK Biobank by BMI category

Variables	**BMI Normal** *n* = 41,369	**BMI Overweight** *n* = 63,731	**BMI Obese-1** *n* = 25,373
Follow-up years, mean (SD)	6.5 (0.9)	6.5 (0.9)	6.5 (0.9)
Age years, mean (SD)	63.9 (2.8)	64.1 (2.8)	64.1 (2.8)
Gender			
Females, *n* (%)	25,778 (62.3)	29,819 (46.8)	12,458 (49.1)
BMI (kg/m^2) n (%)	23.0 (1.5)	27.3 (1.4)	32.0 (1.4)
WHR, n (%)			
WHR lower tertile[1]	23,885 (57.7)	17,239 (27.1)	2,427 (9.6)
WHR intermediate tertile[1]	12,172 (29.4)	24,079 (37.8)	7,222 (28.5)
WHR higher tertile[1]	5,312 (12.8)	22,413 (35.2)	15,724 (62.0)
Alcohol intake frequency, n (%)			
Never	3,109 (7.5)	4,455 (7.0)	2,281 (9.0)
Special occasions only	4,157 (10.1)	6,335 (9.9)	3,481 (13.7)
One-three times a month	3,735 (9.0)	5,922 (9.3)	2,736 (10.8)
Once or twice a week	9,491 (22.9)	15,502 (24.3)	6,355 (25.1)
Three-four times week	9,861 (23.8)	15,595 (24.5)	5,362 (21.1)
Daily or almost daily	11,016 (26.6)	15,922 (25.0)	5,158 (20.3)
Smoking status, n (%)			
Never	25,727 (62.2)	34,289 (53.8)	12,403 (48.9)
Previous	15,642 (37.8)	29,442 (46.2)	12,970 (51.1)

Table S8.1 continued

Variables	**BMI Normal** *n* = 41,369	**BMI Overweight** *n* = 63,731	**BMI Obese-1** *n* = 25,373
Education, n (%)			
None	8,295 (20.1)	16,679 (26.2)	8,183 (32.3)
CSEs	698 (1.7)	1,156 (1.8)	499 (2.0)
GCSEs/O-levels	6,212 (15.0)	9,019 (14.2)	3,396 (13.4)
A-levels/NVQ/HND/HNC	5,505 (13.3)	9,771 (15.3)	4,042 (15.9)
Professional Qualification	6,679 (16.1)	10,149 (15.9)	4,034 (15.9)
College or University degree	13,980 (33.8)	16,957 (26.6)	5,219 (20.6)
Diagnosed disease at baseline, n (%)			
Coronary Heart Disease	1,886 (4.6)	5,207 (8.2)	3,022 (11.9)
Type 2 Diabetes	983 (2.4)	3,162 (5.0)	2,636 (10.4)

[1] WHR was categorised by population and sex-specific tertiles, lower (men <0.91, women < 0.79), intermediate (men 0.91 to <0.96, women 0.79 to <0.85) and higher (men ≥0.96, women ≥0.85)
BMI Normal (BMI 18.5 to <25.0 kg/m^2), BMI Overweight (25.0 to <30.0 kg/m^2) and BMI Obese-1 (30.0 to <35.0 kg/m^2). WHR: Waist-to-hip ratio.

Table S8.2 | Joint association of BMI ranges and WHR tertiles with mortality (*n* = 130,473) and incident coronary heart disease (*n* = 120,358) for participants aged 60 to 69 years from the UK Biobank

BMI category and WHR tertile [1]	**Mortality**	**Coronary heart disease**[2]
	HR (95% CI)	**SHR (95% CI)**
Normal and lower WHR	ref	ref
Normal and intermediate WHR	1.28	1.16
	(1.09, 1.49)	(0.93, 1.44)
Normal and higher WHR	1.33	1.27
	(1.08, 1.65)	(0.95, 1.71)
Overweight	1.22	1.49
	(1.09, 1.36)	(1.29, 1.72)
Overweight and lower WHR	1.12	1.29
	(0.97, 1.30)	(1.07, 1.54)
Overweight and intermediate WHR	1.10	1.51
	(0.97, 1.26)	(1.28, 1.78)
Overweight and higher WHR	1.41	1.64
	(1.25, 1.61)	(1.39, 1.93)
Obese-1	1.42	1.86
	(1.25, 1.61)	(1.59, 2.18)
Obese-1 and lower WHR	1.11	2.10
	(0.82, 1.51)	(1.53, 2.88)
Obese-1 and intermediate WHR	1.32	1.46
	(1.11, 1.57)	(1.16, 1.83)
Obese-1 and higher WHR	1.51	2.02
	(1.32, 1.73)	(1.70, 2.40)

[1] WHR was categorised by population and sex-specific tertiles, lower (men <0.91, women <0.79), intermediate (men 0.91 to <0.96, women 0.79 to <0.85) and higher (men ≥0.96, women ≥0.85)
[2] Analysis for coronary heart disease excludes prevalent cases at baseline *(n* = 10,115).
Survival models (Competing risk models for CHD) were adjusted for age, gender, never or former smoker, alcohol intake, and educational attainment. BMI Normal (BMI 18.5 to <25.0 kg/m^2), BMI Overweight (25.0 to <30.0 kg/m^2) and BMI Obese-1 (30.0 to <35.0 kg/m^2). SHR: Sub-Hazard Ratio; WHR: waist-to-hip ratio.

Chapter 9 Discussion

Table of Contents

List of Tables

9.1. Chapter overview

In this chapter I will firstly review the aim of this thesis and my contributions to the field. The key findings, potential clinical and public health implications, and future research directions will then be discussed. This will be followed by a discussion on the limitations with the datasets (and the associated analyses) and potential measurement errors.

9.2. Summary

The overall aim of my thesis was to clarify whether older persons with obesity are or are not at a greater risk for mortality, coronary heart disease, dementia and diabetes. Additionally, I aimed to clarify whether persons within the BMI Overweight range had the lowest mortality risk**.** As highlighted in **Chapter 1,** the prevalence of obesity in the UK has increased since 1975, and this has been observed across all age groups, which necessitated an updated assessment of the BMI associations with adverse health outcomes in later life. It is well established that younger and middle aged adults within the BMI defined Obese range are at an increased risk for cardiovascular disease, diabetes, dementia and mortality relative to those within the conventional BMI Normal range. In later life, the mortality and dementia risks associated with higher BMI values have been mixed. These equivocal results may be due to several contributors including:

- Inadequate control for confounders e.g. smoking
- Inadequate control for health status e.g. reverse causation
- The BMI referent group
- The inability of BMI to capture body compositional changes with ageing

I used two complimentary datasets to examine the above potential contributors to paradoxical results, the UK CPRD which is representative of the older population, and the UK Biobank which is a volunteer prospective cohort. The advantage of analysing the CPRD is that I had access to electronic health records for registered primary care patients aged ≥60 years which allowed the associations between BMI, CHD, and diabetes to be estimated in narrower age

groups. Furthermore, I had data relating to mortality due to the external linkages for all the studied patients who are known to have died. The advantage of analysing the UK Biobank is that I had access to additional measures of adiposity and body composition which were concurrently measured. Additionally, in the UK Biobank, all lifestyle, socioeconomic, and physical measures were collected on the same date. Compared to other volunteer cohort studies only a few volunteers have opted to leave the study. Both datasets are large scale and thereby stratified analyses could be undertaken whilst maintaining sufficient sample sizes to detect associations. Furthermore, both datasets collected BMI measures within the 21st century, which allows updated quantification of associations with adverse health outcomes.

9.3. New contributions

I have taken this field forward by

- Conducting a meta-analysis on the mortality risk estimates for adults aged ≥65 years within the BMI Overweight and BMI Obese-1 ranges for analyses with no exclusions, specific exclusions (e.g. smokers only) and combined exclusions as well as assessing the choice of the BMI referent group.
- Providing recent mortality estimates for the WHO BMI categories using a large electronic health records dataset (CPRD) of English patients across progressively older age groups and reporting these for 'healthier agers' and 'non-healthier agers' (i.e. accounting for smokers and conditions associated with weight loss).
    - Empirically identifying the major conditions associated with substantial weight loss.
    - Clarifying the number of years of follow-up to exclude to minimise reverse causation.
- Re-defining the BMI referent group, using the CPRD, by modelling the continuous associations with mortality as well as providing recent mortality, incident coronary heart disease, and diabetes risks using this revised referent group for progressively older groups of 'healthier agers'.

- Reporting on the pre-diagnosis weight loss in those diagnosed with dementia. Reporting on the associations between BMI and dementia for the short (0 to <10 years) and long term (10 to <14.9 years).
- Comparing established measures of body fat distribution and body composition to BMI for mortality prediction for 'healthier agers' within the seventh decade of life from the UK Biobank.
- Reporting on the associations between combined measures of BMI and waist-to-hip ratio with mortality and incident coronary heart disease for 'healthier agers' within the seventh decade of life from the UK Biobank.

9.4. Key findings

Several key findings have emerged from the data analyses presented in this thesis, potentially having implications for clinical and public health. The risks for mortality, coronary heart disease, diabetes, and dementia will be discussed. Additionally, I will discuss the BMI referent group. The advantages and disadvantages of using BMI and measures of central adiposity will then be assessed.

Mortality

In **Chapters 3, 4**, **5**, and **7** I focused on the association between BMI and mortality in later life. Firstly, I will discuss the findings using the conventional WHO BMI categories for two separate groups of agers, namely

- non-smokers free of major weight loss associated diseases
- smokers plus those with major diseases associated with weight loss.

This will be followed by a summary of the results using revised BMI referent groups. Subsequently, the results from using alternative measures of adiposity and body composition will be discussed.

Conventional WHO BMI Categories

Non-smokers free of major weight loss associated diseases

In **Chapters 3, 4** and **7** I reported on the mortality risks for the BMI Obese-1 range relative to those within the conventional BMI Normal range. **Table 9.1** details the mortality risks from these chapters. In both **Chapters 3** and **4** I found that without any exclusions the mortality risks were reduced. Additionally, in **Chapter 3** I showed that the mortality risks were not significantly different for singular exclusions or when smokers plus early deaths were excluded. There were increased risks following the exclusion of smokers plus persons with conditions associated with weight loss, which achieved the lowest heterogeneity. However, there were no studies which provided mortality risks for the conventional WHO BMI categories excluding smokers, early deaths plus conditions associated with weight loss. Thus, my analysis in **Chapter 4** applied these three exclusions, which showed increased mortality risks for those aged <75 years and not significantly different risks for those aged 75 to 84 years. One of the limitations of using the CPRD (**Chapter 4**) is that BMI records were only available for 62% of those eligible. Furthermore, height and weight measurements may be taken more frequently for patients with certain health conditions. The UK Biobank was used to address these limitations, as most of the volunteers from this cohort study had height and weight measurements. The results for this analysis were presented in **Chapter 7**, where I showed that mortality risks for the BMI Obese-1 range were in-line with those from the CPRD analysis (**Chapter 4**) for the two youngest age groups, conferring an increased risk.

Table 9.1 | Mortality risks for those within the BMI Obese-1 range relative to those within the conventional BMI Normal range

Exclusions	Chapter 3	Chapter 4	Chapter 7
None	• Reduced aged ≥65 y	• Reduced all age groups (≥60 y)	• NA
Smokers, conditions associated with weight loss and early deaths	• No studies reporting risk estimates aged ≥65 y	• Increased <75 y • Not significantly different 75 to 84 y • Reduced ≥85 y	• Increased 60 to 69 y

In **Chapters 3**, **4** and **7** I also presented findings for the mortality risks for those within the BMI Overweight range relative to those within the conventional BMI Normal range. **Table 9.2** details the mortality risks for these chapters. Again, there were reduced mortality risks reported in both **Chapters 3** and **4** when there were no exclusions for the BMI Overweight range. Additionally, in **Chapter 3** I showed the mortality risks were not significantly different for single or with two exclusions (smokers plus early deaths or smokers and conditions associated with weight loss). There was a lack of studies providing mortality risks for the conventional WHO BMI categories excluding smokers, early deaths plus those with conditions associated with weight loss. Thus, in **Chapter 4** I showed that the mortality risks were not significantly different for those aged <70 years, and reduced for those aged ≥70 years following the application of these three exclusions. Furthermore, the analysis using the UK Biobank in **Chapter 7** showed the risks for those aged 60 to 69 years for the BMI Overweight range were not significantly different to those within the conventional BMI Normal range, albeit with wider confidence intervals.

Table 9.2 | Mortality risks for those within the BMI Overweight range relative to those within the conventional BMI Normal range

Exclusions	Chapter 3	Chapter 4	Chapter 7
None	• Reduced aged ≥65 y	• Reduced all age groups (≥60 y)	• NA
Smokers, conditions associated with weight loss and early deaths	• No studies reporting risk estimates aged ≥65 y	• Not significantly different <70 y • Reduced ≥70 y	• Not significantly different • 60 to 69 y

In **Chapters 4** and **7** I also reported the risks for the BMI Underweight and BMI Obese-2 and Obese-3 ranges. The mortality risks for those aged <70 years from the CPRD (**Chapter 4)** and the UK Biobank (**Chapter 7**) were similar for the BMI Underweight range, BMI Obese-2 and BMI Obese-3 ranges, with increased risks. In **Chapter 4** I also showed that for those aged 70 to <85 years, there were also increased risks for the BMI Underweight, BMI Obese-2 and BMI Obese-3 ranges. For those aged ≥85 years, there were increased risks for the BMI Underweight range only.

Smokers and those with major diseases associated with weight loss

In my analysis of electronic health records for smokers and those with major diseases associated with weight loss, I showed that in all the age-groups relative to those within the conventional BMI Normal range:

- Increased mortality risks for the BMI Underweight range
- Reduced mortality risks for the BMI Overweight range
- Reduced mortality risks for the BMI Obese-1 range
- Reduced mortality risks for the BMI Obese-2 range
- Mortality risks were not significantly different for the BMI Obese-3 range, except for those aged 65 to 69 years with an increased risk

The hazard ratios and 95% confidence intervals did not overlap for the BMI Overweight to Obese-2 ranges, i.e. showed larger reduction in risk compared to the overall sample (e.g. no exclusions) for those aged <85 years. Improved

survival for those within the BMI Obese range has been reported for patients with cancer and heart failure, with factors such as the age at presentation, the severity of the disease, and the use of BMI being suggested for these paradoxical findings (Oreopoulos, *et al*., 2008; Gonzalez, *et al*., 2014; Lennon, *et al*., 2016). Further work is required to understand the reduced mortality risks in these patients (see section **9.6**).

Revised BMI referent groups

As highlighted in **Chapter 1**, one of the proposed suggestions contributing to paradoxical findings is the referent group. I therefore examined this in **Chapters 3** and **5**. In **Chapter 3** I showed mortality risks for the BMI Obese-1 range were not significantly different when early deaths were excluded or when there were no exclusions. There was, however, increased mortality risks when smokers and conditions associated with weight loss were excluded or when smokers, conditions associated with weight loss plus early deaths were excluded. **Table 9.3** details the mortality risks for these chapters for the BMI Obese-1 range with the use of different referent ranges. The results presented in **Chapter 5** for non-smoking 'healthier agers' echoed the findings from **Chapter 3** for the simultaneous exclusions. I did not perform an analysis revising the BMI referent range in the UK Biobank as there did not appear to be a substantial increased mortality risk for those within the lower end of the conventional BMI Normal range when BMI was measured continuously. This could be due to the volunteer participants being healthier compared to the patients within the CPRD.

Table 9.3 | Mortality risks for those within the BMI Obese-1 range relative to those within a revised referent range

Exclusions	**Chapter 3 (referent ≥20.0 to <25.0 kg/m^2)**	**Chapter 5 (referent 23.0 to <25.0 kg/m^2)**	**Chapter 5 (referent 23.0 to <27.0 kg/m^2)**
Smokers, conditions associated with weight loss and early deaths	• Increased aged ≥65 y	• Increased aged <85 y • Not significantly different ≥85 y	• Increased aged <85 y • Not significantly different ≥85 y

In **Chapters 3** and **5** I also presented results for the BMI Overweight range using revised referent groups. In **Chapter 3** I showed mortality risks for the BMI Overweight range were reduced when there were no exclusions. Mortality risks were not significantly different after early deaths were excluded or when there were no exclusions. There was, however, increased mortality risks when smokers, conditions associated with weight loss plus early deaths were excluded, achieving the lowest heterogeneity. In **Chapter 5** I showed there were increased risks for non-smoking 'healthier agers' aged <65 years with a BMI in the range 27.0 to <30.0 kg/m^2 when either the BMI referent group was 23.0 to <25.0 or 23.0 to <27.0 kg/m^2. For those aged 65 to 69 years there was an increased risk when the BMI referent range was 23.0 to <27.0 and the risk was not significantly different when the BMI range 23.0 to <25.0 was used as the referent group. The mortality risks for those aged 70 to <85 years with a BMI in the range 27.0 to <30.0 kg/m^2 were not significantly different to either referent group. In **Chapter 5** I additionally reported on the risks for the BMI referent range 25.0 to <27.0 relative to those within the BMI range 23.0 to <25.0 kg/m^2. The mortality risks were not significantly different for those aged <85 years. For those aged ≥85 years the mortality risks were reduced.

In **Chapter 5** I also showed that the mortality risks for those aged <85 years relative to either a BMI in the range 23.0 to <25.0 or 23.0 to <27.0 kg/m^2:

- Increased for the BMI Underweight range
- Increased for the BMI 18.5 to <23.0 kg/m^2 range
- Increased for the BMI Obese-2 range
- Increased for the BMI Obese-3 range

For those aged ≥85 years there were increased mortality risks for those within the BMI Underweight and BMI range 18.5 to <23.0 kg/m^2 when either the BMI referent range 23.0 to <25.0 or 23.0 to <27.0 kg/m^2 were used. There was a reduced risk for those within the BMI range 27.0 to <30.0 kg/m^2.

The increased risks found for those within the BMI Underweight and lower BMI Normal range across the age-groups could be due to muscle loss with ageing. However, the CPRD did not have additional body compositional records.

Alternative measures of adiposity and body composition for mortality prediction

The CPRD is limited to height and weight measures, with very few measures of alternative measures of adiposity or body composition available. Therefore, I used the UK Biobank to compare established measures of body fat distribution to BMI for mortality prediction for non-smoking 'healthier agers', with the results presented in **Chapter 7**. Measures of central adiposity (waist circumference, waist-to-hip ratio, and waist-to-height ratio) were shown to improve mortality prediction compared to models containing BMI. Increased levels of central adiposity were associated with an increased mortality risk. I found that the correlation for these three measures of central adiposity with BMI was weakest for the waist-to-hip ratio. Additionally, I showed the lowest concordance was found between tertiles of BMI and WHR.

As BMI does not measure the increase in central adiposity with ageing, I therefore combined BMI with a measure of central adiposity for mortality and coronary heart disease prediction, with these results presented in **Chapter 8**. The measure of central adiposity chosen was the waist-to-hip ratio as it conferred to the best fitting model and had the weakest correlation with BMI. Here I aimed to assess whether combining these two measures may more accurately identify those at higher risks for adverse outcomes. Before combining these two measures I showed that the risks for mortality for those within the BMI Overweight range were not significantly different to those within the conventional BMI Normal range, whilst those within the BMI Obese-1 range had increased risks. Those within the BMI Normal range within higher categories of WHR had increased mortality risks. Those within the BMI Overweight range were shown to have increased mortality risks using the BMI Normal range plus lower WHR as the referent group. The point estimates for those within the BMI Overweight range plus higher WHR were much higher to the estimates for the BMI Overweight range only. Thus, the results from these chapters highlight the importance of measuring central adiposity, especially in those considered to have a BMI within the Normal range.

Consistent with previous findings I also showed in **Chapter 7** that increased skeletal mass index was associated with a reduced mortality risk after accounting

for BMI category. However, I did not assess the muscle function or muscle quality for this analysis. Thereby without accounting for this loss in muscle mass and function, my mortality risks could be an underestimation for adiposity, as BMI is a combination of fat mass and fat free mass.

Overall, after accounting for smokers, early deaths, and conditions associated with mortality, I have consistently shown from both the CPRD and the UK Biobank for adults aged 60 to 69 years, using BMI only that there are:

- Increased mortality risks for the BMI Underweight range
- Increased mortality risks for all three classes of Obesity

Decline in mortality risks with advancing age

It is also worth noting that although the BMI mortality risks decline with advancing age, this may be due to the chosen risk measure and the accumulation of competing risk factors (**Chapter 1**). Additionally, some persons may have already died from obesity and thus persons who have survived may be "resistant" to the effect of higher BMI values, which will be accentuated across the progressively older age groups.

Coronary heart disease

In **Chapter 5** I showed the risks for coronary heart disease were raised for those aged <70 years for BMI values ≥27.0 kg/m^2 when either compared to those within the referent group 23.0 to <25.0 kg/m^2 or 23.0 to <27.0 kg/m^2. For those aged 70 to 74 years, there were increased risks for those with BMI values ≥27.0 kg/m^2 and <40.0 kg/m^2, with a non-significant result for those within the BMI Obese-3 range. For those aged 75 to 84 years, there were increased risks for those with BMI values ≥27.0 kg/m^2 and <35.0 kg/m^2, with non-significant results for those within the BMI Obese-2 and BMI Obese-3 ranges. For those aged ≥85 years, there were increased risks only for those within the BMI range 27.0 to <30.0 kg/m^2.

As highlighted in the mortality section, one limitation of the CPRD is that BMI records were unavailable for 38% of those eligible for analysis. I therefore used

the UK Biobank to address this limitation (**Chapter 8**). I showed there were increased risks for CHD for those within the BMI Overweight and Obese-1 ranges relative to those within the BMI Normal range in those aged 60 to 69 years. Interestingly, the CHD risks for the BMI Obese-1 range were much larger in the UK Biobank compared to the CPRD although the referent group was the whole of the conventional BMI Normal range (**Chapter 8**). Similarly, the point estimate was higher for the UK Biobank for the BMI Overweight range compared to the risks reported for the lower and upper ends of the Overweight range. Additionally, in the UK Biobank I showed increased risk of CHD for those who were in the Overweight range with increasing central adiposity, i.e. intermediate and higher tertiles of waist-to-hip ratio, relative to those who have a BMI Normal plus lower waist-to-hip ratio.

Overall, after accounting for smokers, early deaths, and conditions associated with mortality, I have consistently shown from both the CPRD and the UK Biobank for adults aged 60 to 69 years, using BMI only that there are:

- Increased risk of incident CHD for the BMI Obese-1 range

Diabetes

In **Chapter 5** I showed the risk of incident type 2 diabetes was increased for those aged ≥60 years for BMI values ≥25.0 kg/m^2 relative to those within the BMI range 23.0 to <25.0 kg/m^2, using data from the CPRD. This is in line with previous research. The two youngest groups (60 to 64 years and 65 to 69 years) showed no overlap between the confidence intervals for the upper BMI Overweight range and the BMI Obese ranges. There were reduced risks for those aged <85 years with BMI values <23.0 kg/m^2, and risks were not significantly different for those aged ≥85 years.

Dementia

In persons with repeat BMI measures and with incident dementia, weight loss was common during the ten years preceding diagnosis, with 67.7% losing weight. Reduced risks were shown for those within the BMI Overweight and BMI Obese ranges from 0 to <10 years after baseline relative to those within the BMI referent

range 22.5 to <25.0 kg/m^2. However, when examining the risks from 10 to 14.9 years there were increased risks for those within the BMI Obese range. The BMI Overweight range was not significantly different to the referent range**.**

BMI referent group for later life

In terms of the conventional BMI Normal range I have shown that there are increased mortality and dementia risks for those with BMI values <23.0 kg/m^2 from analysis of the CPRD. This increased mortality risk may be due to undiagnosed diseases or from less than optimal body composition. However, in the UK Biobank there did not appear to be a substantially increased mortality risk. This may be due to the shorter follow up, participants being healthier and able to attend the assessment centres. The use of BMI only in later life, however, may miss those at a heightened risk due to central adiposity (**Chapter 8**) or sarcopenia. Thus, more work is required on assessing BMI, additional measures of central adiposity, and sarcopenia with a range of health outcomes across progressively older age groups for defining the optimum BMI and body composition range in later life (see section 9.6).

I showed that there were increased mortality risks only for those within the upper end of the BMI Overweight range (BMI 27.0 to <30.0 kg/m^2) and aged <65 years when only BMI is considered. Mortality risks were similar for those aged 65 to <85 years. Mortality risks for the lower end of the BMI Overweight range (25.0 to <27.0) were not significantly different to those within the higher end of the BMI Normal range (23.0 to <25.0 kg/m^2) for those aged <85 years. For those in the upper end of the BMI Overweight range there was also increased risks for incident CHD for all ages from the CPRD. I showed increased risks of CHD within the UK Biobank for the BMI Overweight range, although in this analysis I did not split this range into a lower and upper range. Furthermore, there was increased risks for incident diabetes for both the lower and upper end of the BMI Overweight range (except for those aged ≥85 years for the lower end) from the analysis of the electronic health records. Thus, these findings do not imply that the BMI Normal range should be redefined to that of the BMI Overweight range for those aged <85 years.

Advantages and disadvantages of measuring BMI and central adiposity

There are many advantages and disadvantages to measuring BMI and measures of central adiposity (waist circumference, waist-to-hip, waist-to-height ratio) both clinically and for research purposes (Snijder *et al.*, 2006; Duren *et al.*, 2008; Ness-Abramof and Apovian, 2008; World Health Organization, 2008; National Academies of Sciences, Engineering, 2016). Advantages of calculating BMI include that minimal to zero training is required to take height and weight measures, with these being easy, quick, inexpensive and non-invasive, and population trends and comparisons can be made as it is one of the most widely used indexes. However, there are several disadvantages to BMI including the inability to differentiate fat and fat free mass and to capture fat redistribution. Age, ethnicity and fitness can modify the correlation between BMI and fat mass. The advantages of the measures of central adiposity include the suitability for monitoring population trends and these measures are inexpensive. Measuring waist circumference only has the advantage of one measure being required, whilst waist-to-hip and waist-to-height allow an adjustment to be made for body shape. Disadvantages of obtaining these measures of central adiposity include the requirement for bodily contact, training is required, differing protocols as to where waist and hip measures should be taken, and the inability to differentiate between subcutaneous and visceral adipose tissues (Snijder *et al.*, 2006; Duren *et al.*, 2008; Ness-Abramof and Apovian, 2008; World Health Organization, 2008; National Academies of Sciences, Engineering, 2016).

9.5. Implications of research findings for clinical and public health practice

When I started my PhD, there was extensive literature claiming that being obese or overweight was beneficial in old age (Al Snih, *et al*., 2007; Flicker, *et al*., 2010; van Uffelen, *et al*., 2010; de Hollander *et al* 2012 b; Flegal, *et al*., 2013; Dixon, *et al*., 2015). If this was true, it would require an abandonment of most public health efforts to prevent obesity in later life (Cetin and Nasr, 2014; Stevens, et al., 2015). Given that 29.9% of females and 32.3% of males aged 65 to 74 years were classified as obese and 35.2% of females and 44.2% of males were classified as

overweight from the Health Survey for England, this would have major implications for public health (Health Survey for England, 2017).

My findings have shown that combining those who are already ill, smokers, and relatively 'healthier agers' can lead to disparate risk estimates, which should be considered when interpreting new research findings. There are several potential implications for clinical and public health practice from the research presented in this thesis:

- Supplement BMI with other measures capturing body composition
- Preventing obesity in later life
- Increased health risks for the BMI Underweight and the lower end of the BMI Normal range

Supplement BMI with other measures capturing body composition

My thesis has highlighted that BMI does not capture body compositional changes with advancing age such as the central redistribution of fat mass which places persons at an elevated mortality risk. Persons within the BMI Normal range are not spared these body compositional changes. Additionally, BMI does not measure the change in fat and fat free mass with ageing. Thus, using BMI only will not capture those who are BMI Normal but obese centrally, and those with sarcopenia. Encompassing measures of central adiposity and sarcopenia in clinical practice could lead to the prevention of a greater proportion of obesity-related adverse events in later life.

In the UK Biobank analyses I showed that 13.4% of the whole sample were BMI Normal but centrally obese (intermediate or higher WHR tertile). Reliance of BMI only would therefore misclassify the risk for these persons who are at an elevated risk for mortality in later life; the use of BMI and a measure of central adiposity should therefore be encouraged for older people. Measures of central adiposity are cheaper and require less time than imaging techniques. Interestingly, the NICE clinical guidelines on obesity 2014 stated "Think about using waist circumference, in addition to BMI, in people with a BMI less than 35 kg/m^2" (NICE Guidelines, 2014). However, in this guideline, only the health risks for persons within the BMI Overweight range and BMI Obese-1 range were documented. My

results have shown that there was an increased mortality risk for those within the BMI Normal range who were also centrally obese (for non-smokers without major conditions associated with weight loss within the seventh decade). At the start of my PhD I ran a pilot analysis to assess if and how many waist circumference measures were within the CPRD, which showed there was few records. The feasibility of clinicians obtaining central adiposity measures needs further research (see section 9.6) and incentives to collecting these measures in primary care should be explored.

Furthermore, my research highlighted a high proportion of those within the BMI Normal range have a low skeletal mass index. In my analysis of the UK Biobank, I showed that for 'healthier agers' aged 60 to 69 years, 58.8% of those within the lowest BMI tertile (BMI ranges 18.56 to 25.91 for males and 18.50 to 24.81 for females) were in the lowest tertile of skeletal mass index. The skeletal mass index ranges for the lowest tertile for males and females were 5.53-8.65 and 4.18-6.10, respectively. These values are below the cut off values for defining sarcopenia mass (<8.87 for males and <6.42 for females) (Cruz-Jentoft, *et al*., 2010). I did not evaluate the muscle function or quality in my analyses. This group of individuals would therefore be a mix of those with pre-sarcopenia (defined by low skeletal mass only) and those with sarcopenia (both low skeletal mass and low grip strength). As highlighted previously, those with sarcopenia have increased mortality risks. There is, therefore, a need to identify individuals with both pre-sarcopenia and sarcopenia.

Low physical activity levels have been shown to be associated with an increased likelihood of sarcopenia (OR 1.36 95% CI 1.11, 1.67) for adults aged ≥65 years (*n* = 18,363) from the Collaborative Research on Ageing in Europe (Tyrovolas, *et al*., 2016). Similarly, a meta-analysis of 7 cross-sectional and cohort studies showed there was a reduced likelihood of sarcopenia for adults who were physically active (OR 0.45 95%CI 0.37, 0.55), in 6 of these studies the participants were aged >60 years (Steffl, *et al*., 2017). Naseeb and Volpe recently reviewed 20 articles published between January 2010 and April 2015 which had examined protein and exercise in relation to sarcopenia. The authors reported that physical function, muscle mass and strength can be improved with a

combination of resistance training plus either supplementation of amino acids or protein, or an increase in dietary protein (Naseeb and Volpe, 2017). Thus, practitioners need to be aware of how to measure sarcopenia and the possible treatment options.

Preventing BMI defined obesity and central obesity in later life

My findings showed that there were increased mortality risks and diabetes risks for the three categories of obesity, for non-smoking adults without major conditions associated with weight loss aged 60 to <85 years, highlighting the significant health implications associated with obesity in later life. Thus, there is a great need to prevent otherwise healthy persons becoming obese, both overall and centrally. This also includes preventing persons within the BMI Normal range becoming centrally obese.

My findings showed that there were increased risks for incident type 2 diabetes for those within the BMI Overweight range for those aged ≥60 years. There were increased risks for incident coronary heart disease for those within the higher end of the BMI Overweight range (27.0 to <30.0 kg/m^2). The risks for mortality for those within the BMI Overweight range tended to not be significantly different to those within the higher end of the BMI Normal range for those aged 60 to <85 years. This makes the decision of whether persons within the BMI Overweight range should lose weight in later life challenging, and more studies are required with a broader range of outcomes (see section 9.6). The emphasis, therefore, may be on maintaining muscle mass and not gaining weight.

Public Health England recently published a framework entitled “All our Health” which calls for healthcare professionals to prevent, improve and promote health and wellbeing at the patient and population level. Included in this framework is guidance on adult obesity, which highlights the importance of obesity in later life (Public Health England, 2015). My research has also reaffirmed this as a crucial age group for obesity prevention. Advice and interventions for weight management may focus on increasing physical activity, modification to diets, lifestyle modifications, prescribing of drugs, and bariatric surgery (Cetin and Nasr, 2014). It should also aim to help older people to put into context media claims that being overweight in old age is good for them.

One of the locations where individuals may receive advice and interventions is at the primary care level. Booth *et al*., (2015) used electronic health records from the CPRD to examine accessibility to weight management interventions for overweight and obese patients aged 30 to 100 years. The authors used a random sample who were registered with a practice between 2005 and 2012 (*n* = 91,143). Access to weight management interventions (advice, referral, or drugs) was greater with increasing BMI values. The lowest access to weight management was reported for the BMI Overweight range, with 8.6% of the males and 9.7% of the females accessing interventions. The highest access to weight management was for the BMI Obese-3 range, with 40.0% of the males and 41.9% of females accessing interventions. Overweight and Obese patients, therefore, may have limited access to weight management interventions, or that advice and interventions have not been documented on patients records (Booth, Prevost, and Gulliford, 2015). There is a need to update and evaluate the access to weight interventions for persons in later life.

A recent meta-analysis of randomised controlled trials which used a dietary intervention for weight loss for obese adults showed a reduced mortality risk (RR 0.82 95% CI 0.71, 0.95) from 34 studies considered high quality. There was no significant difference between those in the treatment arms and control arms for new cardiovascular events (Ma, *et al*., 2017). Bales and Buhr (2008) reviewed 16 weight loss randomized controlled trials which had a duration of ≥6 months for adults aged ≥60 years with BMI values ≥27.0 kg/m^2 and reported that although there were adverse effects on bone mineral density and fat free mass, there were improvements in physical function, osteoarthritis and type 2 diabetes (Bales and Buhr, 2008). Batsis, *et al*., (2017) recently reviewed the evidence for obese adults aged ≥60 years for behavioural based interventions for weight loss, using articles published between January 2005 and October 2015. Six studies met the inclusion criteria, and the duration of the studies ranged from 6 to 18 months. The minimum weight loss documented was 0.5kg and the maximum 10.7kg, with losses greater with interventions focussing on diet. No significant differences in weight loss were documented from exercise only interventions. A combination of interventions focussed on both diet and exercise led to improvements in physical function, self-reported health, bone mineral density, inflammation markers,

cognition markers, glucose homeostasis, and with a reduced decline in muscle mass. The authors, however, stressed there are a limited number of high quality weight loss randomised trials for obesity in later life. Additionally, the outcome of these trials should not focus only on weight loss but also include physical function and self-reported health. Furthermore, none of the trials were carried out in the primary care setting, which is a key area for providing weight loss advice and interventions (Batsis, *et al*., 2017).

Practitioners may have been reluctant to advise or recommend weight loss interventions to adults with obesity in later life due to concerns of accelerated losses of bone mineral density and skeletal mass. Additionally, the willingness or ability of older adults to make lifestyle changes may hamper weight management guidance (Bales and Buhr, 2008; Han, Tajar and Lean, 2011; Decaria, Sharp and Petrella, 2012; Batsis, *et al*., 2017). Interestingly, current NICE guidelines do not separate weight management advice by age (NICE Guidelines, 2014). The emphasis of weight loss may differ with age, with a primary aim of functional and quality of life improvements, although these are applicable for all ages (Han, Tajar and Lean, 2011). Guidance regarding weight should be provided on an individual basis, which considers both health conditions and the individual's weight trajectory, and ensure dietary restriction does not lead to nutrient deficiencies and the conservation of muscle mass (Han, Tajar and Lean, 2011; Decaria, Sharp and Petrella, 2012; Batsis, *et al*., 2017). Continued emphasis should be given to preventing obesity in earlier life due to the body compositional changes with ageing (Han, Tajar and Lean, 2011).

Health risks for the BMI Underweight and the lower end of the BMI Normal range

Although this thesis focussed on whether persons who are overweight or moderately obese (Obese-1) are or are not at an increased risk for mortality and other health outcomes, one of the consistent findings was the increased mortality risk for those within the BMI Underweight range both from the analysis of electronic health records and from the UK Biobank analysis. From the analysis of electronic health records, persons with the BMI lower Normal range (18.5 to <23.0 kg/m^2) had increased mortality and dementia risks. As highlighted

previously, my analysis using the UK Biobank showed that 58.8% of those within the lowest BMI tertile (encompassing the lower BMI Normal range) had pre-sarcopenia or sarcopenia. I did not assess the body composition profile of those within the BMI Underweight range, but it is likely that a high proportion of those would also have sarcopenia. This may have partly accounted for the high mortality rates in the BMI Underweight and lower BMI Normal weight range. Patients should firstly be reviewed to rule out any major weight losing conditions. Focus should then be on gradually increasing, with dietician support as appropriate, the intake of nutrient and calorie dense food, supplements, plus exercise (with a resistance training component) for those within the BMI Underweight and lower BMI Normal range (Starr and Bales, 2015).

9.6. Future research

During my PhD, several additional research areas/questions have emerged as I have progressed throughout my analyses.

Extension to other populations and ethnic groups

There is a need to understand the BMI associations with adverse health outcomes for individuals from different ethnic backgrounds and other populations. Both datasets used in my analyses included patients/participants from the UK (England for CPRD) and the ethnic origin of the participants was predominately 'white' British. Populations differ in the prevalence and treatment of cardiovascular risk factors. Therefore, there is a need to extend the multiple simultaneous approach to assess the associations between recent BMI measures and adverse health outcomes to other ethnic groups and countries to assess the consistency of these findings.

Extension of CPRD analyses

Weight trajectory and cause specific mortality

There is a need to understand the BMI associations and weight trajectories with cause specific mortality. The health outcomes which I predominately focussed on were mortality and dementia due to the mixed research findings with obesity

(**Chapters 4 to 6**). Additionally, I estimated the BMI associations with coronary heart disease, and diabetes (**Chapter 5**). A natural progression from the CPRD analyses would be to estimate the BMI associations for cause-specific mortality. It would be of great interest to model the variation of weight trajectory with incident conditions and cause specific mortality.

Dementia

My analyses presented in **Chapter 6** focussed on the age range 65 to 74 years; additional research is required to clarify the association between BMI groups and dementia for 'healthier agers' above age 74 years. Future work should also consider elucidating the associations between other measures of adiposity with the risk for incident dementia. This could become possible with the additional follow-up data from the UK Biobank. Analyses of specific subtypes of dementia (especially vascular versus Alzheimer's disease) should also be done.

Smokers and those with conditions associated with weight loss

Further work is needed to clarify whether the apparently protective effects of being obese in smokers and those with conditions causing weight loss represents a real effect or whether BMI in such groups is a measure of disease severity, with less severe disease being associated with less weight loss and higher residual adiposity.

Additional outcomes

Assessing additional outcomes of importance to both clinicians and the individuals within the studied age groups need to be identified. For instance, with the ageing population, assessing the association between BMI and frailty may become of greater importance due to the impact on the quality of life. One could use the CPRD to estimate the progression from fit to mild to moderate/severe frailty using the electronic frailty index (Song, Mitnitski and Rockwood, 2010). In **Chapter 7,** I used the UK Biobank to compare established measures of body fat distribution and components of body composition to BMI for mortality prediction with more follow-up data the magnitudes of the associations of these measures with alternative health outcomes such as coronary heart disease and diabetes would be possible. Currently, the UK Biobank is in the process of linking the

volunteers' data to their primary health care records and this would allow type 2 diabetes and many other primary care diagnosed conditions to be used as health outcomes (e.g. osteoarthritis in the knee).

Qualitative research

There is a need to identify the feasibility of health care practitioners additionally measuring central adiposity. My analysis using the UK Biobank (**Chapter 8**) highlighted the importance of combining BMI and WHR (as a measure of central adiposity). Therefore, future research is required to assess what are the barriers and enablers to measuring central adiposity in primary care in later life.

Additional measures of adiposity

My analysis in the UK Biobank showed that the mortality model fit was substantially improved compared to the BMI model, hence measures of the adipose tissue distribution may improve the mortality model fit further. The UK Biobank is currently in the process of collecting imaging data from both DXA and MRI scans with an aim of measuring 100,000 UK Biobank volunteers. In my analyses using the UK Biobank I showed that measures of central adiposity (waist circumference, WHR, and WHtR) were associated with an increased mortality risk. The MRI liver scans and abdominal scans would enable associations to be estimated for liver fat percentage, subcutaneous and visceral adipose tissue with adverse health outcomes on a much larger scale than prior analyses. It would be interesting to compare the mortality model fit using the subcutaneous and visceral adipose tissue to those using measures of central adiposity, and gender differences with fat distribution. There has been a limited amount of research using adipose tissue distribution and these analyses have not been restricted to 'healthier' subset or concurrently compared measures (Murphy *et al.*, 2014; Koster *et al.*, 2015). Furthermore, the prognostic value of measures capturing body compositional changes needs to be assessed across progressively older age groups as I was only able to present findings for those within the seventh decade of life.

Additional statistical methods

There is potential to improve our understanding of the associations between BMI and health outcomes in later life by using different statistical methods. My analysis used the CPRD and the UK Biobank with one time point measure only for BMI and the confounders (except for documenting weight change). The primary aim of my analyses was to use one off measures. However, future studies could use time series analyses which would account for changes in baseline characteristics and weight. This could be extended to subsets of patients with specific changes during follow-up. My analyses from the UK Biobank (and CPRD) have been observational designs. The UK Biobank has provided genetic data for >150,000 volunteers so far and is in the process of releasing the remaining data for the whole cohort. This large scale of genetic data lends itself to Mendelian randomization analysis which provides evidence on causal influences. My future research will involve analysing genetic risk scores (summation of the number of BMI risk alleles) with mortality and health outcomes in later life.

Effect of weight change

There is still a need to see how weight change affects survival/ healthy survival and the development of adverse health conditions in later life using different study designs. My analyses showed that for 'healthier agers' persons within the BMI Obese-1 range had increased risks for CHD, diabetes, and mortality. Future research, therefore, needs to clarify what are the health implications of persons in later life intentionally changing from a higher weight (BMI) to a lower weight e.g. is their risk for CHD reduced. Additional work would, therefore, be required on the feasibility and the appropriate intervention to reduce weight. Consideration would be required to ensure maintenance of muscle mass and persons do not become malnourished.

9.7. Limitations of my meta-analysis

A key limitation to the meta-analysis in **Chapter 3** is that there was large heterogeneity for some of the analyses I presented. I realise the level of adjustment for confounding within each study will have implications on the pooled results. Whilst this was not in the remit of this analysis as my focus was on the

inclusion and exclusion criteria, future analyses should consider the study level characteristics. For my meta-analysis I extracted mortality risk estimates, where possible, from models which have not adjusted for intermediate factors, e.g. hypertension. However, mortality risk estimates from four analyses which had adjusted for intermediate factors had to be extracted (see **Chapter 3**). A sensitivity analysis was carried out excluding these four analyses where possible. Furthermore, my review included English language publications only and therefore I may have missed some additional analyses.

9.8. Limitations using the CPRD and presented analyses

There are several limitations with analysing the data from the CPRD. One of the main limitations with the CPRD is that there was no measures of body fat distribution or components of body composition. Additionally, only a subset of patients had repeat BMI measures to categorise weight loss. There was no available data on whether the weight loss was intentional. As noted in **Chapter 2**, one of the key limitations with the CPRD is that health records are not primarily collected for research purposes (Herrett *et al.*, 2015). The recording of a medical event is determined by the general practitioner and data may be collected during routine health checks or opportunistically. Lifestyle factors could be documented more often in subsets of patients with certain health conditions (Welch and Bartlett, 2014; Herrett *et al.*, 2015). Variables are not documented at the same baseline date thereby historical records must be used. Additionally, it may be assumed that patients without pre-specified Read Codes for the chosen health outcomes may be free of the disease or condition of interest (Herrett *et al.*, 2015). Patients could be missing data but using complete cases may result in biased estimates. However, this could be due to differences in Read Codes selected by health practitioners, the documentation of symptoms and diagnoses in free text, and from patients avoiding primary care consultations. The quality and completeness of medical records may be altered with new or updates to clinical guidelines and financial incentives. A physical activity measure was available for 55.3% of patients aged 60 to 64 years; 55.6% aged 65 to 69 years; 56.1% of patients aged 70 to 74 years; 55.8% of patients aged 75 to 84 years; and 55.9% for patients aged ≥85 years and this was based on Read Codes rather than a

validated questionnaire. Therefore, my models may not have adequately accounted for physical activity. Additionally, in this analysis residual confounding may have persisted in the models as the exclusion of conditions most closely associated with weight loss did not capture all patients with substantial weight loss. Furthermore, there may have been residual confounders; for instance, in my dementia analysis there was no measure of educational attainment.

9.9. Limitations using the UK Biobank and presented analyses

The UK Biobank is a healthy volunteers study and has a relatively short follow-up period with a maximum of 8.3 years. In a similar manner to the CPRD, there is also the issue that some participants may be missing data. Volunteers could opt to select the "prefer not to answer" or "do not know" for the touchscreen questionnaire (UK Biobank, 2013). To date, there is no data available on primary care consultations (although this is planned to be linked in the future). This could lead to an underestimation of diagnoses which may be more commonly recorded at the primary care level such as diabetes. As highlighted in **Chapter 2,** the UK Biobank participants had lower mortality risks and cancer risks compared to the general population. Again, there may have been residual confounding in the presented analyses.

9.10. Measurement errors

Several measurement errors should be considered in light of the presented analyses. I used BMI as a surrogate measure of adiposity, however as noted in previous chapters, this metric is unable to detect body compositional changes with ageing. Batsis *et al.*, (2016) showed that with advancing age the proportion of adults correctly classified as BMI Obese declined with age (Batsis *et al.*, 2016). This could explain the attenuation of the mortality risks observed across the progressively older age groups from the CPRD. As noted earlier, only a subset of the CPRD patients and none of the UK Biobank volunteers had repeat BMI measures. Using a single BMI measure could result in underestimation of the mortality risks. I had no data regarding BMI fluctuations over the life course, the age of onset of obesity or the number of years the patients/volunteers were in a specific BMI range. Stokes and Preston (2016) showed that the mortality model

fit was improved by using a person's maximum BMI rather than using the BMI measure from the survey baseline date (Stokes and Preston, 2016b). However, in primary care a general practitioner may only have information on a single BMI measure so it is still important to assess the prognostic utility of one BMI measure. Furthermore, I was unable to account for changes in risk factor levels across time. In both datasets, I excluded persons with recent cancer, dementia and heart failure. In the CPRD I excluded the first 3.9 years of follow-up and in the UK Biobank I excluded the first 1.9 years (due to a shorter follow-up period and healthier volunteers). This length of follow-up period excluded may not have captured subclinical diseases (e.g. dementia) with a long latency period. Furthermore, there may be residual confounding due to unknown or unmeasured risk factors (e.g. diet). As highlighted earlier, a physical activity measure was missing for a substantial proportion of patients.

9.11. Conclusion

Concurrent with the trend of rising obesity is an ageing population. It is well established that younger and middle aged adults within the BMI Obese range are at an increased risk for mortality relative to those within the conventional BMI Normal range. However, mortality risks for older persons within the BMI Obese range have been mixed. This presents challenges on interpreting the evidence and can impact management and treatment of obesity in later life. My thesis has highlighted that multiple factors contribute to the obesity paradox and the need to separate out smokers and weight losers. Additionally, there is a need to measure central adiposity with BMI. I have shown the heterogeneity of older adults can result in disparate risk estimates for the association between BMI and health outcomes. My analyses have shown that the obesity paradox can be largely accounted for by the pooling of the relatively healthy, smokers, those with conditions associated with weight loss plus the chosen BMI referent group. 'Healthier agers' within the BMI Obese-1 range do not have a mortality advantage relative to those within the BMI referent range, 23.0-24.9 kg/m^2; for those aged 60 to 84 years there is an increased mortality risk. I also documented no support for reduced dementia risks for those within the BMI Obese range. Additionally, I found persons within the BMI Obese-1 range have increased risks for incident

diabetes and coronary heart disease (up to age 84 years). I provided additional evidence, using the UK Biobank, that reliance on BMI measures only may miss those at increased risk for health outcomes due to central adiposity; persons within the optimum BMI range may not necessarily have 'ideal' fat distribution. Additionally, my findings do not imply that the BMI Normal range should be redefined to that of the BMI Overweight range for adults aged <85 years. My results provide no support, in relatively healthy older adults, for the hypothesised obesity paradox in later life. There is a great need to prevent persons becoming obese in later life and to dispel the claims that obesity in later life provides a mortality advantage.

Chapter 10 References

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